Title: HMG COA REDUCTASE MEDIATED MODULATION OF NEUROGENESIS

<table>
<thead>
<tr>
<th>Combination</th>
<th>CI</th>
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<tr>
<td>Atorvastatin + Buspirone</td>
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<td>Atorvastatin + Azakenpaullone</td>
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<td>Atorvastatin + Folic Acid</td>
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<td>Atorvastatin + Serotonin</td>
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(57) Abstract: The instant disclosure describes methods of treating diseases and conditions of the central and peripheral nervous system including by stimulating or increasing neurogenesis, neuroproliferation, and/or neurodifferentiation. The disclosure includes compositions and methods based on use of an HMGCPR modulating agent, optionally in combination with one or more other neurogenic agents, to stimulate or increase a neurogenic response and/or to treat disease.
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HMG COA REDUCTASE MEDIATED MODULATION OF NEUROGENESIS

CROSS-REFERENCES TO RELATED APPLICATIONS

[0001] This application is related to U.S. Provisional Patent Application 60/826,710 filed September 22, 2006 which is incorporated herein by reference in its entirety.

FIELD OF THE DISCLOSURE

[0002] The instant disclosure relates to compositions and methods for treating diseases and conditions of the central and peripheral nervous system by, for example, stimulating or increasing a neurogenic response, using a 3-hydroxy-3-methyl-glutaryl-CoA reductase (HMGCR) inhibitor, optionally in combination with one or more other neurogenic agents. The disclosure includes methods based on the application of the modulator and/or the combination to stimulate or increase a neurogenic response, and/or the formation of new nerve cells and/or neurodifferentiation.

BACKGROUND OF THE INVENTION


[0004] Citation of the above documents is not intended as an admission that any of the foregoing is pertinent prior art. Statements about these documents do not constitute any admission as to the correctness of the dates or contents of these documents.

BRIEF SUMMARY OF THE INVENTION

[0005] Disclosed herein are compositions and methods for the prophylaxis and treatment of diseases, conditions and injuries of the central and peripheral nervous systems by stimulating or increasing neurogenesis. Aspects of the methods, and activities of the compositions, include increasing or potentiating neurogenesis in cases of a disease, disorder, or condition of the nervous system. Embodiments of the disclosure include methods of treating a neurodegenerative disorder, neurological trauma including brain or central nervous system trauma and/or recovery therefrom, depression, anxiety, psychosis, learning and memory disorders, and ischemia of the central and/or peripheral nervous systems. In other embodiments, the disclosed methods are used to improve cognitive outcomes and mood disorders.

[0006] In one aspect, methods of modulating, such as by stimulating or increasing, neurogenesis are disclosed. The neurogenesis may be at the level of a cell or tissue. The cell or tissue may be present in an animal subject or a human being, or alternatively be in an in vitro or ex vivo setting. In some embodiments, neurogenesis is stimulated or increased in a neural cell or tissue, such as that of the central or peripheral nervous system of an animal or human being. In cases of an animal or human, the methods may be practiced in connection with one or more disease, disorder, or condition of the nervous system as present in the animal or human subject. Thus, embodiments disclosed herein include methods of treating a disease, disorder, or condition by administering at least one neurogenesis modulating agent having activity against HMG Coenzyme A Reductase (HMGCR or, alternatively, HMGCoAR), hereinafter referred to as a "an HMGCR agent". An HMGCR agent may be formulated or used alone, or in combination with one or more additional neurogenic agents.

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[0007] While an HMGCR agent may be considered a "direct" agent in that it has direct activity against HMGCR by interactions therewith, the disclosure includes an HMGCR agent that may be considered an "indirect" agent in that it does not directly interact with HMGCR. Thus, an indirect agent acts on HMGCR indirectly, or via production, generation, stability, or retention of an intermediate agent which directly interacts with HMGCR.

[0008] Embodiments of the disclosure include a combination of an HMGCR agent and one or more other neurogenic agents disclosed herein or known to the skilled person. An additional neurogenic agent as described herein may be a direct HMGCR agent, an indirect HMGCR agent, or a neurogenic agent that does not act, directly or indirectly, through HMGCR. Thus in some embodiments, an additional neurogenic agent is one that acts, directly or indirectly, through a mechanism other than HMGCR. An additional neurogenic agent as described herein may be one which acts through a known receptor or one which is known for the treatment of a disease or condition. The disclosure further includes a composition comprising a combination of an HMGCR agent with one or more other neurogenic agents.

[0009] In a second aspect, the disclosure includes a method of lessening and/or reducing a decline or decrease of cognitive function in a subject or patient. In some cases, the method may be applied to maintain and/or stabilize cognitive function in the subject or patient. The method may comprise administering an HMGCR agent, optionally in combination with one or more other neurogenic agents, to a subject or patient in an amount effective to lessen or reduce a decline or decrease of cognitive function.

[0010] In an additional aspect, the disclosure includes a method of treating mood disorders with use of an HMGCR agent, optionally in combination with one or more other neurogenic agents. In some embodiments, the method may be used to moderate or alleviate a mood disorder in a subject or patient. Non-limiting examples include a subject or patient having, or diagnosed with, a disease or condition as described herein. In other embodiments, the method may be used to improve, maintain, or stabilize mood in a subject or patient. Of course the method may be optionally combined with any other therapy or condition used in the treatment of a mood disorder.

[0011] In a third aspect, the disclosed methods include identifying a patient suffering from one or more diseases, disorders, or conditions, or a symptom thereof, and administering to the patient an HMGCR agent, optionally in combination with one or more other neurogenic
agents, as described herein. In some embodiments, a method including identification of a subject as in need of an increase in neurogenesis, and administering to the subject an HMGCR agent, optionally in combination with one or more other neurogenic agents is disclosed herein. In other embodiments, the subject is a patient, such as a human patient.

[0012] Another aspect of the disclosure describes a method including administering an HMGCR agent, optionally in combination with one or more other neurogenic agents, to a subject exhibiting the effects of insufficient amounts of, or inadequate levels of, neurogenesis. In some embodiments, the subject may be one that has been subjected to an agent that decreases or inhibits neurogenesis. Non-limiting examples of an inhibitor of neurogenesis include opioid receptor agonists, such as a mu receptor subtype agonist like morphine. In other cases, the need for additional neurogenesis is that detectable as a reduction in cognitive function, such as that due to age-related cognitive decline, Alzheimer's Disease, epilepsy, or a condition associated with epilepsy as non-limiting examples.

[0013] In a related manner, a method may include administering an HMGCR agent, optionally in combination with one or more other neurogenic agents, to a subject or person that will be subjected to an agent that decreases or inhibits neurogenesis. Non-limiting embodiments include those where the subject or person is about to be administered morphine or another opioid receptor agonist, like another opiate, and so about to be subject to a decrease or inhibition of neurogenesis. Non-limiting examples include administering an HMGCR agent, optionally in combination with one or more other neurogenic agents, to a subject before, simultaneously with, or after the subject is administered morphine or other opiate in connection with a surgical procedure.

[0014] In a fifth aspect, the disclosure includes methods for preparing a population of neural stem cells suitable for transplantation, comprising culturing a population of neural stem cells (NSCs) in vitro, and contacting the cultured neural stem cells with an HMGCR agent, optionally in combination with one or more other neurogenic agents. In some embodiments, the stem cells are prepared and then transferred to a recipient host animal or human. Non-limiting examples of preparation include 1) contact with an HMGCR agent, optionally in combination with one or more other neurogenic agents, until the cells have undergone neurogenesis, such as that which is detectable by visual inspection or cell counting, or 2) contact with an HMGCR agent, optionally in combination with one or more other neurogenic agents, until the cells have been sufficiently stimulated or induced toward or
into neurogenesis. The cells prepared in such a non-limiting manner may be transplanted to a subject, optionally with simultaneous, nearly simultaneous, or subsequent administration of another neurogenic agent to the subject. While the neural stem cells may be in the form of an in vitro culture or cell line, in other embodiments, the cells may be part of a tissue which is subsequently transplanted into a subject.

[0015] In yet another aspect, the disclosure includes methods of modulating, such as by stimulating or increasing, neurogenesis in a subject by administering an HMGCR agent, optionally in combination with one or more other neurogenic agents. In some embodiments, the neurogenesis occurs in combination with the stimulation of angiogenesis which provides new cells with access to the circulatory system.

[0016] Certain embodiments provides a composition, comprising: a first neurogenic agent comprising an inhibitor of 3-hydroxy-3-methyl-glutaryl-CoA reductase (HMGCR); and a second neurogenic agent, wherein the first and second agents are in combination in a single formulation, and wherein the second agent is not an antidepressant or, preferably, a known antidepressant. In certain embodiments, the composition further comprises a pharmaceutically acceptable carrier. In certain embodiments, the first and second agents are combined together in a unit dose.

[0017] In certain embodiments, the first neurogenic agent is an the inhibitor of HMGCR; and the second agent is a muscarinic receptor modulator, a phosphodiesterase (PDE) modulator, histone deacetylase (HDAC) modulator, a gamma-aminobutyric acid (GABA) receptor modulator, a thyrotropin-releasing hormone (TRH) receptor agonist, a weight modulating agent, a glutamate receptor modulator, an amphetamine, a peroxisome proliferator-activated receptor (PPAR) modulator, a nootropic agent, an α-amino-3-hydroxy-5-methylisoxazole-4- propionic acid (AMPA) receptor modulator, an opioid receptor modulator, an androgen receptor modulating agent, a rho kinase inhibitor, a glycogen synthase kinase 3 (GSK-3) modulating agent, an acetylcholinesterase (AChE) inhibitor, an epilepsy treating agent, a dual sodium and calcium channel modulating agent, a calcium channel modulating agent, a melanocortin receptor modulating agent, an angiotensin II receptor modulating agent, a neurosteroid agent, a non-steroidal anti-inflammatory agent, a migraine treating agent, a nuclear hormone receptor modulating agent, a nicotinic receptor modulating agent, a cannabinoid receptor modulating agent, a fatty acid amide hydrolase (FAAH) antagonist, a nitric oxide modulating agent, a prolactin modulating agent, an anti-
viral agent, a calcitonin receptor agonist, an antioxidant agent, a norepinephrine receptor modulating agent, a carbonic anhydrase modulating agent, a catechol-o-methyltransferase (COMT) modulating agent, a hedgehog modulating agent, an inosine monophosphate dehydrogenase (IMPDH) modulating agent, or a sigma receptor modulating agent.

[0018] In certain embodiments, the first neurogenic agent is atorvastatin (CAS RN 134523-00-5), cerivastatin (CAS RN 145599-86-6), crilvastatin (CAS RN 120551-59-9), fluvastatin (CAS RN 93957-54-1), fluvastatin sodium (CAS RN 93957-55-2), simvastatin (CAS RN 79902-63-9), lovastatin (CAS RN 75330-75-5), pravastatin (CAS RN 81093-37-0), pravastatin sodium (CAS RN 81131-70-6), rosuvastatin (CAS RN 287714-41-4), or simvastatin (CAS RN 79902-63-9); and the second agent is a thyrotropin-releasing hormone (TRH) receptor agonist, a weight modulating agent, a glutamate receptor modulator, an amphetamine, a peroxisome proliferator-activated receptor (PPAR) modulator, a nootropic agent, an α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) receptor modulator, an opioid receptor modulator, an androgen receptor modulating agent, a rho kinase inhibitor, a glycogen synthase kinase 3 (GSK-3) modulating agent, an acetylcholinesterase (AChE) inhibitor, an epilepsy treating agent, a dual sodium and calcium channel modulating agent, a calcium channel modulating agent, a melanocortin receptor modulating agent, an angiotensin II receptor modulating agent, a neurosteroid agent, a non-steroidal anti-inflammatory agent, a migraine treating agent, a nuclear hormone receptor modulating agent, a nicotinic receptor modulating agent, a cannabinoid receptor modulating agent, a fatty acid amide hydrolase (FAAH) antagonist, a nitric oxide modulating agent, a prolactin modulating agent, an anti-viral agent, a calcitonin receptor agonist, an antioxidant agent, a norepinephrine receptor modulating agent, a carbonic anhydrase modulating agent, a catechol-o-methyltransferase (COMT) modulating agent, a hedgehog modulating agent, an inosine monophosphate dehydrogenase (IMPDH) modulating agent, or a sigma receptor modulating agent.

[0019] In certain embodiments, the composition further comprises a third agent which is niacin or ezetimibe; and the second agent is a thyrotropin-releasing hormone (TRH) receptor agonist, a weight modulating agent, a glutamate receptor modulator, an amphetamine, a peroxisome proliferator-activated receptor (PPAR) modulator, a nootropic agent, an α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) receptor modulator, an opioid receptor modulator, an androgen receptor modulating agent, a rho kinase inhibitor, a glycogen
synthase kinase 3 (GSK-3) modulating agent, an acetylcholinesterase (AChE) inhibitor, an epilepsy treating agent, a dual sodium and calcium channel modulating agent, a calcium channel modulating agent, a melanocortin receptor modulating agent, an angiotensin II receptor modulating agent, a neurosteroid agent, a non-steroidal anti-inflammatory agent, a migraine treating agent, a nuclear hormone receptor modulating agent, a nicotinic receptor modulating agent, a cannabinoid receptor modulating agent, a fatty acid amide hydrolase (FAAH) antagonist, a nitric oxide modulating agent, a fatty acid amide hydrolase (FAAH) antagonist, a nitric oxide modulating agent, a prolactin modulating agent, a carbonic anhydrase modulating agent, a catechol-o-methyltransferase (COMT) modulating agent, a hedgehog modulating agent, an inosine monophosphate dehydrogenase (IMPDH) modulating agent, or a sigma receptor modulating agent.

[0020] In certain embodiments, the second neurogenic agent has the property of enhancing a neurogenic effect of the first neurogenic agent. In certain embodiments, the first and the second agents act synergistically.

[0021] In certain embodiments, the first agent is atorvastatin (CAS RN 134523-00-5); and the second agent is buspirone (CAS RN 36505-84-7), ribavirin (CAS RN 36791-04-5), tacrine (CAS RN 321-64-2), azakenpaullone, serotonin, or azasetron (CAS RN 123039-99-6), or any combination thereof.

[0022] The chemical structure of azakenpaullone is set forth below.

[0023] Certain embodiment provide a method of treating a nervous system disorder in an animal subject, preferably a mammalian subject, and more preferably a human subject, in need thereof, the method comprising administering a neurogenic amount of the composition of claim 1 to the mammalian subject, thereby treating the nervous system disorder.

[0024] In certain embodiments, the nervous system disorder is related to a nerve cell trauma, a psychiatric condition, a neurologically related condition, or any combination thereof.
In certain embodiments, the nervous system disorder is a neural stem cell disorder, a neural progenitor cell disorder, a degenerative disease of the retina, an ischemic disorder, or any combination thereof.

In certain embodiments, the psychiatric condition is an affective disorder, depression, major depression, treatment refractory depression, hypomania, panic attacks, anxiety, excessive elation, bipolar depression, bipolar disorder, seasonal mood disorder, schizophrenia, psychosis, lissencephaly syndrome, anxiety, an anxiety syndrome, an anxiety disorder, a phobia, stress, a stress syndrome, a cognitive function disorder, aggression, drug abuse, alcohol abuse, an obsessive compulsive behavior syndrome, a borderline personality disorder, non-senile dementia, post-pain depression, post-partum depression, cerebral palsy, post traumatic stress disorder (PTSD), or any combination thereof.

In certain embodiments, the psychiatric condition is depression. In certain embodiments, the psychiatric condition is post traumatic stress disorder (PTSD).

In certain embodiments, the nerve cell trauma is from an injury or a surgery. In certain embodiments, the injury or the surgery is related to: retinal injury or surgery, cancer treatment, infection, inflammation, an environmental toxin, or any combination thereof.

In certain embodiments, the neurologically related condition is a learning disorder, autism, an attention deficit disorder, narcolepsy, a sleep disorder, a cognitive disorder, epilepsy, temporal lobe epilepsy, or any combination thereof.

In certain embodiments, the subject is a human.

Certain embodiments provide a method of increasing neurodifferentiation of a vertebrate cell or a vertebrate tissue, the method comprising contacting the cell or the tissue with a composition comprising: a first neurogenic agent comprising an inhibitor of an HMGCR; and a second neurogenic agent, wherein the first and second agents are in combination in a single formulation, and wherein the second agent is not an antidepressant or, preferably, a known antidepressant, in an amount that is effective to increase neurodifferentiation of the cell or the tissue. In certain embodiments, the cell or tissue is mammalian or, preferably, human. In certain embodiments, the contacting step is performed in vitro.

Certain embodiments provide a method of increasing neurogenesis of a vertebrate cell or a vertebrate tissue, the method comprising contacting the cell or the tissue with a
composition comprising: a first neurogenic agent comprising an inhibitor of an HMGCR; and a second neurogenic agent, wherein the first and second agents are in combination in a single formulation, and wherein the second agent is not an antidepressant or, preferably, a known antidepressant, in an amount that is effective to increase neurogenesis of the cell or the tissue.

In certain embodiments, the cell or tissue is mammalian or, preferably, human. In certain embodiments, the contacting step is performed in vitro.

[0033] Certain embodiments provide a first neurogenic agent and a second neurogenic agent in combination in a single formulation, wherein the first agent is an inhibitor of 3-hydroxy-3-methyl-glutaryl-CoA reductase (HMGCR); and the second agent is a selective serotonin reuptake inhibitor (SSRI). In certain embodiments, the first agent is atorvastatin (CAS RN 134523-00-5); and the second agent is the SSRI. In certain embodiments, the first agent is atorvastatin; and the second agent is fluoxetine, duloxetine, sertraline, paroxetine, fluvoxamine, citalopram, or escitalopram.

[0034] Certain embodiments provide a composition comprising a first neurogenic agent and a second neurogenic agent in combination in a single formulation, wherein the first agent is an inhibitor of 3-hydroxy-3-methyl-glutaryl-CoA reductase (HMGCR); and the second agent is buspirone, ribavirin, tacrine, azakenpaullone, folic acid, or serotonin. In certain embodiments, the first neurogenic agent is atorvastatin; and the second neurogenic agent is buspirone, ribavirin, tacrine, azakenpaullone, folic acid, or serotonin.

[0035] Certain embodiments provide a composition comprising a first neurogenic agent and a second neurogenic agent combined in a single formulation, wherein the first neurogenic agent is an inhibitor of 3-hydroxy-3-methyl-glutaryl-CoA reductase (HMGCR); and the second neurogenic agent is a 5-HT1a agonist, an antiviral agent, an acetylcholinesterase inhibitor, a GSK-3 inhibitor (preferably a GSK-3β inhibitor), or a one-carbon metabolism modulator. In certain embodiments, the first neurogenic agent is an inhibitor of 3-hydroxy-3-methyl-glutaryl-CoA reductase (HMGCR); and the second neurogenic agent is buspirone, ribavirin, tacrine, azakenpaullone, or folic acid.

[0036] The details of additional embodiments are set forth in the accompanying drawings and the description below. Other features, objects, and advantages of the embodiments will be apparent from the drawings and detailed description, and from the claims.
DETAILED DESCRIPTION OF THE DRAWINGS

[0037] FIG. 1 is a dose-response curve showing effect of the HMGCR inhibitor atorvastatin on neuronal differentiation. Data is presented as the percentage of the neuronal positive control, with basal media values subtracted. EC$_{50}$ was observed at an atorvastatin concentration of 0.0031 µM in test cells, compared to 4.7 µM for the positive control compound.

[0038] FIG. 2 is a dose-response curve showing effect of the neurogenic agents atorvastatin (HMGCR inhibitor) and buspirone (5-HT1a receptor agonist) in combination on neuronal differentiation of human neural stem cells compared to the effect of either agent alone. When run independently, atorvastatin was tested in a concentration response curve ranging from 0.00001 µM to 0.03 µM, and buspirone was tested in a response curve ranging from 0.01 - 31.6 µM. In combination, the compounds were combined at a 1:1000 ratio at each point (for example, the first point in the combined curve consisted of a test of 0.00001 µM atorvastatin and 0.01 µM buspirone). Data is presented as the percentage of the neuronal positive control, with basal media values subtracted. When used alone, EC$_{50}$ was observed at an atorvastatin concentration of 0.0031 µM or a buspirone concentration of 5.8 µM in test cells. When used in combination, neurogenesis is greatly enhanced: EC$_{50}$ was observed at a combination of atorvastatin and buspirone at concentrations of 0.0006 µM and 0.6 µM respectively, resulting in a synergistic combination index of 0.32.

[0039] FIG. 3 is a dose-response curve showing effect of the neurogenic agents atorvastatin (HMGCR inhibitor) and ribavirin (antiviral, IMPDH inhibitor) in combination on neuronal differentiation of human neural stem cells compared to the effect of either agent alone. When run independently, atorvastatin was tested in a concentration response curve ranging from 0.00001 µM to 0.03 µM, and ribavirin was tested in a response curve ranging from 0.01 - 31.6 µM. In combination, the compounds were combined at a 1:1000 ratio at each point (for example, the first point in the combined curve consisted of a test of 0.00001 µM atorvastatin and 0.01 µM ribavirin). Data is presented as the percentage of the neuronal positive control, with basal media values subtracted. When used alone, EC$_{50}$ was observed at an atorvastatin concentration of 0.0031 µM or a ribavirin concentration of 3.8 µM in test cells. When used in combination, neurogenesis is greatly enhanced: EC$_{50}$ was observed at a combination of atorvastatin and ribavirin at concentrations of 0.0003 µM and 0.3 µM respectively, resulting in a synergistic combination index of 0.18.
FIG. 4 is a dose-response curve showing effect of the neurogenic agents atorvastatin (HMGCR inhibitor) and tacrine (acetylcholinesterase inhibitor) in combination on neuronal differentiation of human neural stem cells compared to the effect of either agent alone. When run independently, atorvastatin was tested in a concentration response curve ranging from 0.00001 µM to 0.03 µM, and tacrine was tested in a response curve ranging from 0.01 - 31.6 µM. In combination, the compounds were combined at a 1:1000 ratio at each point (for example, the first point in the combined curve consisted of a test of 0.00001 µM atorvastatin and 0.01 µM tacrine). Data is presented as the percentage of the neuronal positive control, with basal media values subtracted. When used alone, EC₅₀ was observed at an atorvastatin concentration of 0.0031 µM or a tacrine concentration of 7.4 µM in test cells. When used in combination, neurogenesis is greatly enhanced: EC₅₀ was observed at a combination of atorvastatin and tacrine at concentrations of 0.0009 µM and 0.89 µM respectively, resulting in a synergistic combination index of 0.44.

FIG. 5 is a dose-response curve showing effect of the neurogenic agents atorvastatin (HMGCR inhibitor) and azakenpaullone (GSK3β inhibitor) in combination on neuronal differentiation of human neural stem cells compared to the effect of either agent alone. When run independently, atorvastatin was tested in a concentration response curve ranging from 0.00001 µM to 0.03 µM, and azakenpaullone was tested in a response curve ranging from 0.001 - 3.16 µM. In combination, the compounds were combined at a 1:100 ratio at each point (for example, the first point in the combined curve consisted of a test of 0.00001 µM atorvastatin and 0.001 µM azakenpaullone). Data is presented as the percentage of the neuronal positive control, with basal media values subtracted. When used alone, EC₅₀ was observed at an atorvastatin concentration of 0.00031 µM or an azakenpaullone concentration of 1.1 µM in test cells. However, addition of azakenpaullone resulted in a maximum percent of positive control neuronal differentiation greater than 100%. When the maximum percent of positive control was fixed to a common 120% for all conditions tested (based upon the maximum concentration of azakenpaullone alone), EC₅₀ was observed at an atorvastatin concentration of 0.004 µM or an azakenpaullone concentration of 0.33 µM in test cells. When used in combination, neurogenesis is greatly enhanced: EC₅₀ was observed at a combination of atorvastatin and azakenpaullone at concentrations of 0.0008 µM and 0.75 µM respectively, resulting in a synergistic combination index of 0.47.

FIG. 6 is a dose-response curve showing effect of the neurogenic agents atorvastatin (HMGCR inhibitor) and folic acid in combination on neuronal differentiation of human
neural stem cells compared to the effect of either agent alone. When run independently, atorvastatin was tested in a concentration response curve ranging from 0.00001 μM to 0.03 μM, and folic acid was tested in a response curve ranging from 0.01 - 31.6 μM. In combination, the compounds were combined at a 1:1000 ratio at each point (for example, the first point in the combined curve consisted of a test of 0.00001 μM atorvastatin and 0.01 μM folic acid). Data is presented as the percentage of the neuronal positive control, with basal media values subtracted. When used alone, EC_{50} was observed at an atorvastatin concentration of 0.0031 μM or a folic acid concentration of 4.8 μM in test cells. When used in combination, neurogenesis is greatly enhanced: EC_{50} was observed at a combination of atorvastatin and serotonin at concentrations of 0.0005 μM and 0.52 μM respectively, resulting in a synergistic combination index of 0.28.

Fig. 7 is a dose-response curve showing effect of the neurogenic agents atorvastatin (HMGCR inhibitor) and serotonin (in vitro model of the effects of a serotonin reuptake inhibitor, such as fluoxetine) in combination on neuronal differentiation of human neural stem cells compared to the effect of either agent alone. When run independently, atorvastatin was tested in a concentration response curve ranging from 0.00001 μM to 0.03 μM, and serotonin was tested in a response curve ranging from 0.01 - 31.6 μM. In combination, the compounds were combined at a 1:1000 ratio at each point (for example, the first point in the combined curve consisted of a test of 0.00001 μM atorvastatin and 0.01 μM serotonin). Data is presented as the percentage of the neuronal positive control, with basal media values subtracted. When used alone, EC_{50} was observed at an atorvastatin concentration of 0.0031 μM or a serotonin concentration of 4.5 μM in test cells. When used in combination, neurogenesis is greatly enhanced: EC_{50} was observed at a combination of atorvastatin and serotonin at concentrations of 0.0005 μM and 0.5 μM respectively, resulting in a synergistic combination index of 0.29.

Figures 8-10 show the effects of atorvastatin, fluoxetine and the combination of the two drugs on BrdU positive cells within the granule cell layer of the dentate gyrus. Male F344 rats were dosed 1x per day for 28-days with vehicle (n = 12 per dose group, p.o.), 5.0 mg/kg fluoxetine (n = 12 per dose group, p.o.), 15.0 mg/kg fluoxetine (n = 12 per dose group, p.o.), 10.0 mg/kg atorvastatin (n = 12 per dose group, p.o.) or the combination of fluoxetine (5.0 mg/kg, p.o.) + atorvastatin (10.0 mg/kg, p.o.). Figure 8 shows BrdU positive cell counts within the granule cell layer of the dentate gyrus. Data are presented as percent change in
BrdU positive cells per cubic mm dentate gyrus. Atorvastatin alone significantly increased
the number of BrdU positive cells.

[0045] Figure 9 shows the rate of neuronal differentiation of BrdU+ cells within the granule
cell layer of the dentate gyrus. Data are presented as the percentage of cells colabeled for
BrdU and the mature neuronal marker NeuN within the dentate gyrus. The combination of
atorvastatin + fluoxetine resulted in a significant increase in the percentage of Brdu+/Neun+
cells.

[0046] Figure 10 shows the number of new neurons within the granule cell layer of the
dentate gyrus. Both atorvastatin alone and the combination of atorvastatin with fluoxetine
resulted in a significant increase in the number of new neurons.

[0047] Figure 11 shows the combination indices for the listed combinations of neurogenic
agents as they act on neural tissue. A combination index (CI) of less than one indicates that
the first and second neurogenic agents act synergistically when used in combination. All first
and second neurogenic agents listed in Figure 11 are highly synergistic in action when
combined.

DETAILED DESCRIPTION OF THE INVENTION

DEFINITIONS OF SELECTED TERMS

[0048] "Neurogenesis" is defined herein as proliferation, differentiation, migration and/or
survival of a neural cell in vivo, in vitro, or ex vivo. In various embodiments, the neural cell
is an adult, fetal, or embryonic neural stem cell or population of cells. The cells may be
located in the central nervous system or elsewhere in an animal or human being (e.g., the
peripheral nervous system). The cells may also be in a tissue, such as neural tissue. In certain
embodiments, the neural cell is an adult, fetal, or embryonic progenitor cell or population of
cells, or a population of cells comprising a mixture of stem cells and progenitor cells. Neural
cells include, without limitation, all neural stem cells, all neural progenitor cells, and all
neural precursor cells. Neural cells are found, without limitation in the central and peripheral
nervous systems. Neurogenesis includes, without limitation neurogenesis as it occurs during
normal development, adulthood, and/or neural regeneration that occurs following disease,
damage or therapeutic intervention, such as by the treatments described in certain
embodiments herein. Neurogenesis can occur from the differentiation of all types of stem cells (see below for non-limiting examples).

"Astrogenesis," as defined herein, refers to the activation, proliferation, differentiation, migration and/or survival of an astrocytic cell in vivo, in vitro, or ex vivo. Non-limiting examples of astrocytic cells include astrocytes, activated microglial cells, astrocyte precursors and potentiated cells, and astrocyte progenitor and derived cells. In some embodiments, the astrocyte is an adult, fetal, or embryonic astrocyte or population of astrocytes. The astrocytes may be located in the central nervous system or elsewhere in an animal or human being. The astrocytes may also be in a tissue, such as neural tissue. In some embodiments, the astrocyte is an adult, fetal, or embryonic progenitor cell or population of cells, or a population of cells comprising a mixture of stem and/or progenitor cells, that is/are capable of developing into astrocytes. Astrogenesis includes the proliferation and/or differentiation of astrocytes as it occurs during normal development, as well as astrogenesis that occurs following disease, damage or therapeutic intervention. Astrocytes or their precursors or derivatives are found, without limitation in the central and peripheral nervous systems. Astrogenesis can occur from the differentiation of all types of stem cells (see below for non-limiting examples).

A "neurogenic agent" is defined herein as a chemical agent or biological reagent that can sensitize, promote, stimulate, or increase the amount, degree, or nature of a neurogenic response in vivo, ex vivo, or in vitro relative to the amount, degree, or nature of neurogenesis in the absence of the agent or reagent. A neurogenic agent (and therefore a neurogenic response) is understood as an chemical agent or biological reagent that increases the relative ratio of neurogenesis to astrogenesis based upon the activation, proliferation, differentiation, migration and/or survival of stem cells, neural cells, and/or astrocytes (including embryonic, fetal, and/or adult cells). For example, a neurogenic agent may increase neurogenesis, decrease astrogenesis, or both. Thus, in one example, the ratio of the number of nerve cells to astrocytes is increased by administration of the agent or chemical reagent to cells or tissues in vivo, in vitro, or ex vivo. In certain embodiments, treatment with a neurogenic agent increases neurogenesis or the ratio of neurogenesis to astrogenesis (i.e., the neurogenic response), by at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 40%, at least about 50%, at least about 75%, at least about 100%, at least about 200% (2 fold), at least about 300% (3 fold), at least about 400% (4 fold), preferably at least about 500% (5 fold), more
preferably at least about 1000% (10 fold), or still more preferably more in comparison to the amount, degree, and/or nature of neurogenesis or neurogenic response in the absence of the agent, under the conditions of the method used to detect or determine neurogenesis. In certain embodiments, the one or more additional neurogenic agents do not elicit a neurogenic response at the dose provided, but do have the property of enhancing the neurogenic response in combination with the first neurogenic agent comprising an inhibitor of 3-hydroxy-3-methyl-glutaryl-CoA reductase (HMGCR) (the second agent acts as a sensitizing agent). In certain embodiments, the neurogenic effect of the composition is greater than the sum of the neurogenic effects of each neurogenic agent when the neurogenic agent is used independently (a synergistic effect, preferably tested in vitro). A neurogenic response can occur from the differentiation of all types of stem cells (see below for non-limiting examples of stem cells types).

[0051] "Neurodifferentiation" is defined herein as the divergence in structure and function of different cell types as they become specialized during development of the cell or tissue, organ, or organism in which the cell resides. Neurodifferentiation can occur in vivo, in vitro, or ex vivo. In various embodiments, the neural cell is an adult, fetal, or embryonic stem cell (preferably a neural stem cell) or population of cells. In certain embodiments, the stem cells include totipotent, pluripotent, multipotent, and/or unipotent stem cells. The cells may be located in the central nervous system or elsewhere in an animal or human being (e.g., the peripheral nervous system). The cells may also be in a tissue, such as neural tissue. In certain embodiments, the neural cell is an adult, fetal, or embryonic progenitor cell or population of cells, or a population of cells comprising a mixture of stem cells and progenitor cells. Neural cells include, without limitation, all neural stem cells, all neural progenitor cells, and all neural precursor cells. Neural cells are found, without limitation, in the central and peripheral nervous systems. Neurodifferentiation includes, without limitation, differentiation as it occurs during normal development, adulthood, and/or neural regeneration that occurs following disease, damage or therapeutic intervention, such as by the treatments described in certain embodiments herein.

[0052] The term "stem cell" as used herein, refers to an undifferentiated cell that is capable of self-renewal and differentiation into all different cells types and/or tissues in a subject.
The term "neural stem cell (NSC)," as used herein, refers to an undifferentiated cell that is capable of self-renewal and differentiation into neurons, and neuroglia (examples of neuroglia (glia cells) include astrocytes and oligodendrocytes).

The term "progenitor cell", as used herein, refers to a cell derived from a stem cell that is not itself a stem cell. Progenitor cells are capable of differentiating into one or more, but not all cell and/or tissue types in a subject.

The term "neural progenitor cell", as used herein, refers to a cell derived from a stem cell that is not itself a stem cell. Neural progenitor cells are capable of differentiating into neurons and neuroglia.

"Potency" of a stem cell is a term that specifies the differentiation potential (the potential to differentiate into different cell types) of the stem cell.

"Totipotent" stem cells are produced from the fusion of an egg and sperm cell. Cells produced by the first few divisions of the fertilized egg are also totipotent. Totipotent cells can differentiate into embryonic and extraembryonic cell types.

"Pluripotent" stem cells are the descendants of totipotent cells and can differentiate into cells derived from any of the three germ layers.

"Multipotent" stem cells can produce only cells of a closely related family of cells (e.g., hematopoietic stem cells differentiate into red blood cells, white blood cells, platelets, etc.).

"Unipotent" stem cells can produce only one cell type, but have the property of self-renewal which distinguishes them from non-stem cells.

The term "subject" as used herein (e.g., as in a subject of treatment in certain embodiments), refers to a non-human mammal or, preferably, to a human.

The term "non-human mammal" as used herein refers to any non-human mammal (non-limiting examples include: primates, canines, felines, domesticated livestock, such as cattle, swine, sheep, or goats, zoo animals and other animals for exhibition, ruminants or carnivores, such as dogs, cats, birds, horses, cattle, sheep, goats, marine mammals, penguins, deer, elk, or foxes).

The term "cognitive function" refers to mental processes of a non-human mammal or a human subject relating to information gathering and/or processing; the understanding,
reasoning, and/or application of information and/or ideas; the abstraction or specification of ideas and/or information; acts of creativity, problem-solving, and intuition; and mental processes such as learning, perception, and/or awareness of ideas and/or information. The mental processes are distinct from those of beliefs, desires, and the like. In some embodiments, cognitive function may be assessed, and thus optionally defined, via one or more tests or assays for cognitive function. Non-limiting examples of a test or assay for cognitive function include CANTAB (see for example Fray et al. "CANTAB battery: proposed utility in neurotoxicology." Neurotoxicol Teratol 1996; 18(4):499-504), Stroop Test, Trail Making, Wechsler Digit Span, or the CogState computerized cognitive test (see also Dehaene et al. "Reward-dependent learning in neuronal networks for planning and decision making." Prog Brain Res 2000; 126:2 17-29; Iverson et al. "Interpreting change on the WAIS-III/WMS-III in clinical samples," Arch Clin Neuropsychol 2001; 16(2): 183-91; and Weaver et al. "Mild memory impairment in healthy older adults is distinct from normal aging." Brain Cogn 2006;60(2): 146-55). Cognitive function preferably refers to the mental processes of learning and/or memory and can be measured in learning and/or memory task evaluations.

[0064] "IC\textsubscript{50}\" as used herein is a measure of concentration which is the half maximal inhibitory concentration of an inhibitory agent. For example, IC\textsubscript{50} represents the concentration of an inhibitor that is required for 50% inhibition of its target (e.g., an enzyme, cell, cell receptor or a microorganism). In another example, IC\textsubscript{50} measures how much of a particular agent is needed to inhibit some biological process by 50%. For competition binding assays and functional antagonist assays, IC\textsubscript{50} is a common summary measure of the dose-response curve.

[0065] The term "EC\textsubscript{50}\" stands for half maximal effective concentration, and refers to the concentration of an agent which induces a response halfway between the baseline and maximum. EC\textsubscript{50} is commonly used as a measure of drug potency. The EC\textsubscript{50} of a graded dose response curve, therefore, represents the concentration of a compound where 50% of its maximal effect is observed. The EC\textsubscript{50} of a quantal dose response curve represents the concentration of a compound where 50% of a population exhibits a response. For agonist/stimulator assays, EC\textsubscript{50} is a common summary measure of the dose response curve.

[0066] IC\textsubscript{50} and EC\textsubscript{50} values can be assayed in a variety of environments, including cell-free environments, cellular environments (e.g., cell culture assays), multicellular
environments (e.g., in tissues or other multicellular structures), and/or in vivo. In some embodiments, one or more neurogenic agents individually have a IC_{50} or a EC_{50} value of less than about 10 µM, less than about 1 µM, or less than about 0.1 µM or lower. In other embodiments, a first neurogenic agent in a combination with a second neurogenic agent has an IC_{50} or EC_{50} of less than about 1000 nM, of less than about 500 nM, of less than about 100 nM, of less than about 50 nM, less than about 10 nM, or less than about 1 nM or lower.

[0067] The presence of synergy is determined by use of a combination index (CI). The CI based on the IC_{50} or EC_{50} which is used to determine whether a pair of compounds has an additive, synergistic (greater than additive), or antagonistic effect when run in combination. The CI is a quantitative measure of the nature of drug interactions, comparing the EC_{50} (or IC_{50}) of two compounds, when each is assayed alone, to the EC_{50} (or IC_{50}) of each compound when assayed in combination. The combination index (CI) is equal to the following formula:

\[
CI = \frac{C1 + C2 + (CI \times IC2)}{IC1 + IC2}
\]

wherein C1 and C2 are the concentrations of a first and a second compound, respectively, resulting in 50% activity in neuronal differentiation when assayed in combination; and IC1 and IC2 are the concentrations of each compound resulting in 50% activity when assayed independently. A CI of less than 1 indicates the presence of synergy; a CI equal to 1 indicates an additive effect; and a CI greater than 1 indicates antagonism between the two compounds.

The above is based on the selection of EC_{50} (or IC_{50}) as the point of comparison for the two compounds. The comparison is not limited by the point used, but rather the same comparison may be made at another point, such as EC_{20}, EC_{30}, EC_{40}, EC_{60}, EC_{70}, EC_{80} or any other EC (or IC) value above, below, or between any of those points.

[0068] In certain embodiments, compounds described herein that contain a chiral center include all possible stereoisomers of the compound, including compositions comprising the racemic mixture of the two enantiomers, as well as compositions comprising each enantiomer individually, substantially free of the other enantiomer. Thus, for example, contemplated herein is a composition comprising the S enantiomer of a compound substantially free of the R enantiomer, or the R enantiomer substantially free of the S enantiomer. If the named compound comprises more than one chiral center, the scope of the present disclosure also includes compositions comprising mixtures of varying proportions between the
diastereomers, as well as compositions comprising one or more diastereomers substantially free of one or more of the other diastereomers. By "substantially free" it is meant that the composition comprises less than 25%, 15%, 10%, 8%, 5%, 3%, 2%, or less than 1% of the minor enantiomer or diastereomer(s). Methods for synthesizing, isolating, preparing, and administering various stereoisomers are known in the art.

[0069] A "polymorphism" or "polymorph" is a given crystal structure of a substance that can crystallize with more than one crystal structure. Different polymorphs of the same compound can have quite different physical properties, such as shelf-life and solubility. Some of these differences in physical properties can lead to differences in therapeutic efficacy. In certain embodiments, the invention provides an essentially pure version of either crystal form. The term "essentially pure" means that either form contains less than 10 weight percent of another polymorph form, preferably less than 5 weight percent.

[0070] "Synergistic" refers to the interaction of discrete agents (e.g., neurogenic agents) or conditions such that the total effect is greater than the sum of the individual effects.

[0071] A "dose" is the measured quantity of a therapeutic agent to be taken at one time.

[0072] The term "treating" as used herein comprises prophylactic treatment (in certain embodiments); stabilizing a decline in neurodifferentiation (in certain embodiments); stabilizing a neurogenic decline (in certain embodiments); enhancing, stimulating, or increasing a neurogenic effect (in certain embodiments); enhancing, stimulating, or increasing neurodifferentiation (in certain embodiments); and enhancing, stimulating, or increasing neurogenesis (in certain embodiments). In certain embodiments, treating includes prevention, amelioration, alleviation, and/or elimination of the disease, disorder, or condition being treated or one or more symptoms of the disease, disorder, or condition being treated, as well as improvement in the overall well being of a subject, as measured by objective and/or subjective criteria. In some embodiments, treating is used for reversing, attenuating, minimizing, suppressing, or halting undesirable or deleterious effects of, or effects from the progression of, a disease, disorder, or condition of the central and/or peripheral nervous systems. In other embodiments, the method of treating may be advantageously used in cases where additional neurogenesis would replace, replenish, or increase the numbers of cells lost due to injury or disease as non-limiting examples. The amount of a first neurogenic agent or combination with one or more other neurogenic agents may be any that results in a measurable relief of a disease condition like those described herein. As a non-limiting
example, an improvement in the Hamilton depression scale (HAM-D) score for depression may be used to determine (such as quantitatively) or detect (such as qualitatively) a measurable level of improvement in the depression of a subject. Non-limiting examples of symptoms that may be treated with the methods described herein include abnormal behavior, abnormal movement, hyperactivity, hallucinations, acute delusions, combativeness, hostility, negativism, withdrawal, seclusion, memory defects, sensory defects, cognitive defects, and tension. Non-limiting examples of abnormal behavior include irritability, poor impulse control, distractibility, and aggressiveness. Outcomes from treatment with the disclosed methods include improvements in cognitive function or capability in comparison to the absence of treatment.

[0073] As used herein a "first neurogenic agent" comprises an HMGCR modulating agent.

[0074] The term "HMGCR modulating agent" as used herein includes a neurogenic agent that elicits an observable response upon contacting a 3-hydroxy-3-methyl-glutaryl-CoA reductase (HMGCR) enzyme. "HMGCR agents" useful in the methods described herein include compounds, modulators, or agents that, under certain conditions, may act as: agonists (i.e., agents able to elicit one or more biological responses of HMGCR); partial agonists (i.e., agents able to elicit one or more biological responses of HMGCR to a less than maximal extent, e.g., as defined by the response of the receptor to an agonist); and/or inhibitors (agents able to inhibit one or more characteristic responses of HMGCR. A preferred HMGCR modulating agent is an inhibitor of HMGCR.

[0075] In some embodiments, the HMGCR agent(s) used in the methods described herein are substantially inactive with respect to other enzymes or various receptors (i.e., non-HMGCR enzymes); such as muscarinic receptors, 5-HT receptors, dopamine receptors, epinephrine receptors, histamine receptors, glutamate receptors, and the like. However, in other embodiments, HMGCR agent(s) are active against one or more additional enzymes or receptors.

[0076] The term "depression" as used herein includes any and all depression syndromes or disorders including, for example, depression, bipolar depression, major depression, treatment refractory depression, or any combination thereof.
NEUROGENIC AGENTS AND METHODS OF USE THEREOF

[0077] In certain embodiments the present invention provides one or more neurogenic agents and methods of use thereof. In certain embodiments, two or more neurogenic agents provided in combination in a single formulation and other embodiments provide methods of using a neurogenic agent or combinations of neurogenic agents.

[0078] In certain embodiments, where a method comprises contacting a neural cell with an HMGCR inhibitor, the result may be an increase in neurodifferentiation. The method may be used to potentiate a neural cell for proliferation, and thus neurogenesis, via the one or more other agents used with the HMGCR agent in combination. Thus the disclosure includes a method of maintaining, stabilizing, stimulating, or increasing neurodifferentiation in a cell or tissue by use of an HMGCR inhibiting agent, optionally in combination with one or more other neurogenic agents that also increase neurodifferentiation. The method may comprise contacting a cell or tissue with an HMGCR inhibiting agent, optionally in combination with one or more other neurogenic agents, to maintain, stabilize stimulate, or increase neurodifferentiation in the cell or tissue.

[0079] The disclosure also includes a method comprising contacting the cell or tissue with an HMGCR inhibiting agent in combination with one or more other neurogenic agents where the combination stimulates or increases proliferation or cell division in a neural cell. The increase in neuroproliferation may be due to the one or more other neurogenic agents and/or to the HMGCR inhibiting agent. In some cases, a method comprising such a combination may be used to produce neurogenesis in a population of neural cells. In some embodiments, the cell or tissue is in an animal subject, a vertebrate subject, a mammalian subject, or a human patient as described herein. Non-limiting examples include a human patient treated with chemotherapy and/or radiation, or other therapy or condition which is detrimental to cognitive function; or a human patient diagnosed as having epilepsy, a condition associated with epilepsy, or seizures associated with epilepsy. Administration of an HMGCR inhibiting agent, optionally in combination with one or more other neurogenic agents, may be before, after, or concurrent with, another agent, condition, or therapy. It is preferred that the one or more other neurogenic agents ("the second agent") is not an antidepressant or, more preferably, a known antidepressant.
Compositions

A 3-hydroxy-3-methyl-glutaryl-CoA reductase (HMGCR) Enzyme Inhibiting Agent and Combinations Therewith

[0080] Certain embodiments provide a composition, comprising: a first neurogenic agent comprising an HMGCR inhibiting agent; and a second neurogenic agent, wherein the first and second agents are in combination in a single formulation. It is understood that the formulation is not limited to only two agents as third, fourth, or more neurogenic agents can be combined with the formulation. A variety of classes of second (or third, etc.) agents are described herein below.

[0081] Non-limiting examples of an inhibitor of HMGCR include atorvastatin (CAS RN 134523-00-5), cerivastatin (CAS RN 145599-86-6), crilvastatin (CAS RN 120551-59-9), fluvastatin (CAS RN 93957-54-1) and fluvastatin sodium (CAS RN 93957-55-2), simvastatin (CAS RN 79902-63-9), lovastatin (CAS RN 75330-75-5), pravastatin (CAS RN 81093-37-0) or pravastatin sodium (CAS RN 81131-70-6), rosuvastatin (CAS RN 287714-41-4), and simvastatin (CAS RN 79902-63-9). Formulations containing one or more of such inhibitors may also be used in a combination. Non-limiting examples include formulations comprising lovastatin such as Advicor® (an extended-release, niacin containing formulation) or Altocor® (an extended release formulation); and formulations comprising simvastatin such as Vytorin® (combination of simvastatin and ezetimibe).

[0082] In certain embodiments, the second agent is not an inhibitor of the HMGCR enzyme.

[0083] In certain embodiments, the second neurogenic agent does not necessarily have apparent neurogenic activity in and of itself at a given dose, but, rather, the neurogenic activity is observed when combined with an inhibitor of HMGCR which results in enhanced, or even synergistic neurogenic activity compared to the activity of each agent alone.

[0084] Certain embodiments provide a composition comprising an inhibitor of HMGCR for use in the disclosed methods of the present invention.

[0085] In certain embodiments, a neurogenic agent or combination of neurogenic agents is combined with a pharmaceutically acceptable carrier.

[0086] In certain embodiments, a neurogenic agent includes pharmaceutically acceptable salts, derivatives, prodrugs, and metabolites, thereof. Methods for preparing and
administering salts, isomers, polymorphs, derivatives, prodrugs, and metabolites are well known in the art.

[0087] In certain embodiments, the separate effect of multiple neurogenic agents assayed independently or used in therapy independently is less than the combined effect when two or more agents are used in combination, but the effect is not necessarily synergistic. This is referred to herein as an "enhanced effect" of the combined agents or combination therapy. In certain embodiments, the first and second neurogenic agents act synergistically when used in neurogenic assays or therapies. In certain embodiments showing enhanced effects and/or synergistic effects, one or more agents in a combination may be used in a lower dose compared to using the neurogenic agent alone. In certain embodiments, combination treatments (i.e., use of composition comprising a combination of neurogenic agents) lead to advantages such as, without limitation, reductions in side effects, dosage levels, dosage frequency, treatment duration, safety, tolerability, and/or other factors.

[0088] In certain embodiments, neurogenic agents used in combination are used sequentially. In certain embodiments, the methods of the disclosure are not limited in the sequence of administration. In certain preferred embodiments, neurogenic agents used in combination are used together in a single formulation. In certain embodiments, a combination of neurogenic agents is provided together in a single unit dose.

[0089] In certain embodiments, the HMGCR agent includes one or more pharmaceutically acceptable salts, derivatives, prodrugs, and metabolites of the agent. Methods for preparing and administering salts, derivatives, prodrugs, and metabolites of various agents are well known in the art.

[0090] In certain embodiments, compounds described herein that contain a chiral center include all possible stereoisomers of the compound, including compositions comprising the racemic mixture of the two enantiomers, as well as compositions comprising each enantiomer individually, substantially free of the other enantiomer. Thus, for example, contemplated herein is a composition comprising the S enantiomer of a compound substantially free of the R enantiomer, or the R enantiomer substantially free of the S enantiomer. If the named compound comprises more than one chiral center, the scope of the present disclosure also includes compositions comprising mixtures of varying proportions between the diastereomers, as well as compositions comprising one or more diastereomers substantially free of one or more of the other diastereomers. By "substantially free" it is meant that the
composition comprises less than 25%, 15%, 10%, 8%, 5%, 3%, or less than 1% of the minor enantiomer or diastereomer(s). Methods for synthesizing, isolating, preparing, and administering various stereoisomers are known in the art.

[0091] As described herein, an HMGCR agent, optionally in combination with one or more other neurogenic agents, is administered to a subject to result in neurogenesis. A combination may thus be used to treat a disease, disorder, or condition of the disclosure.

[0092] Methods for assessing the nature and/or degree of neurogenesis in vivo and in vitro, for detecting changes in the nature and/or degree of neurogenesis, for identifying neurogenesis modulating agents, for isolating and culturing neural stem cells, and for preparing neural stem cells for transplantation or other purposes are disclosed, for example, in U.S. Provisional Application No. 60/697,905, and U.S. Publication Nos. 2005/0009742 and 2005/0009847, 20050032702, 2005/0031538, 2005/0004046, 2004/0254152, 2004/0229291, and 2004/0185429.

Neurogenic Agents for Combination with an HMGCR Modulating Agent

[0093] In certain embodiments herein a first neurogenic agent comprising an HMGCR modulating agent is combined with a second (or third, etc.) neurogenic agent, preferably in a single formulation, but alternatively, provided separately. The following sections describe, in a non-limiting manner, compounds and classes of compounds that are useful in combination with the first neurogenic agent comprising an HMGCR agent. Without being bound to theory, it is understood that each of the following agents is a neurogenic agent (which neurogenic character may only be revealed in combination with an HMGCR modulating agent, in certain embodiments).

[0094] It is also understood that any one agent or more than one agents described below can be explicitly excluded from a preferred embodiment or a claim. In certain embodiments, the composition does not include an antidepressant agent. In certain embodiments, the composition does not include an agent that is known to be an antidepressant at the time of filing.

Antidepressant Agents

[0095] In certain embodiments, one or more antidepressant agents are useful in combination with a first neurogenic agent of the present invention. In preferred embodiments an antidepressant agent is explicitly excluded from a neurogenic composition of the present
invention. In more preferred embodiments any known antidepressant agent is explicitly excluded from a neurogenic composition of the present invention. Non-limiting examples of antidepressant agents as known to the skilled person, and useful, in certain embodiments, herein, include the following.

SSRIs (selective serotonin reuptake inhibitors), such as fluoxetine (Prozac®; described, e.g., in U.S. Pat. 4,314,081 and 4,194,009), citalopram (Celexa; described, e.g., in U.S. Pat. 4,136,193), escitalopram (Lexapro; described, e.g., in U.S. Pat. 4,136,193), fluvoxamine (described, e.g., in U.S. Pat. 4,085,225) or fluvoxamine maleate (CAS RN: 61718-82-9) and Luvox®, paroxetine (Paxil®; described, e.g., in U.S. Pat. 3,912,743 and 4,007,196), or sertraline (Zoloft®; described, e.g., in U.S. Pat. 4,536,518), or alaproclate; the compound nefazodone (Serozone®; described, e.g., in U.S. Pat. 4,338,317); a selective norepinephrine reuptake inhibitor (SNRI) such as reboxetine (Edronax®), atomoxetine (Strattara®), milnacipran (described, e.g., in U.S. Pat. 4,478,836), sibutramine or its primary amine metabolite (BTS 54 505), amoxapine, or maprotiline; a selective serotonin & norepinephrine reuptake inhibitor (SSNRI) such as venlafaxine (Effexor; described, e.g., in U.S. Pat. 4,761,501), and its reported metabolite desvenlafaxine, or duloxetine (Cymbalta; described, e.g., in U.S. Pat. 4,956,388); a serotonin, noradrenaline, and dopamine "triple uptake inhibitor", such as DOV 102,677 (see Popik et al. "Pharmacological Profile of the "Triple" Monoamine Neurotransmitter Uptake Inhibitor, DOV 102,677." Cell Mol Neurobiol, 2006 Apr 25; electronically published ahead of print), DOV 216,303 (see Beer et al. "DOV 216,303, a "triple" reuptake inhibitor: safety, tolerability, and pharmacokinetic profile." J Clin Pharmacol, 2004 44(12): 1360-7), DOV 21,947 ((+)-l-(3,4-dichlorophenyl)-3-azabicyclo-(3.1.0)hexane hydrochloride), see Skolnick et al. "Antidepressant-like actions of DOV 21,947: a "triple" reuptake inhibitor." Eur J Pharmacol, 2003 461(2-3):99-104), NS-2330 or tesofensine (CAS RN 402856-42-2), or NS 2359 (CAS RN 843660-54-8); and agents like dehydroepiandrosterone (DHEA), and DHEA sulfate (DHEAS), CP-122,721 (CAS RN 145742-28-5).

Additional non-limiting examples of antidepressant agents include a tricyclic compound such as clomipramine, dosulepin or dothiepin, lofepramine (described, e.g., in 4,172,074), trimipramine, protriptyline, amitriptyline, desipramine(described, e.g., in U.S. Pat. 3,454,554), doxepin, imipramine, or nortriptyline; a psychostimulant such as dextroamphetamine and methylphenidate; an MAO inhibitor such as selegiline (Emsam®); an ampakine such as CX516 (or Ampalex, CAS RN: 154235-83-3), CX546 (or 1-(1,4-
benzodioxan-6-ylcarbonyl)piperidine), and CX614 (CAS RN 19174-13-5) from Cortex Pharmaceuticals; a VIb antagonist such as SSR149415 ((2S,4R)-1-[5-Chloro-l-[(2,4-dimethoxyphenyl)sulfonfyl]-3-(2-methoxy-phenyl)-2-oxo-2,3-dihydro-lH-indol-3-yl]-4-hydroxy-N,N-dimethyl-2-pyrrolidine carboxamide),

[0098] 1-[(beta-mercapto-beta, beta-cyclopentamethylenepropionic acid), 2-O-ethyltyrosine, 4-valine] arginine vasopressin (d(CH₂)₅[Tyr(Et₂)]VAVP (WK 1-1), 9-desglycine[l-[(beta-mercapto-beta, beta-cyclopentamethylenepropionic acid), 2-O-ethyltyrosine, 4-valine] arginine vasopressin desGly9d(CH₂)₅[Tyr(Et₂)]-VAVP (WK 3-6), or 9-desglycine [l-[(beta-mercapto-beta, beta-cyclopentamethylenepropionic acid)], 2-D-(O-ethyl)tyrosine, 4-valine] arginine vasopressin desGly9d(CH₂)₅[D-Tyr(Et₂)]VAVP (AO 3-21); a corticotropin-releasing factor (CRF) R antagonist such as CP-1 54,526 (structure disclosed in Schulz et al. "CP-154,526: a potent and selective nonpeptide antagonist of corticotropin releasing factor receptors." PNAS U.S.A. 1996 93(19):10477-82), NBI 30775 (also known as R121919 or 2,5-dimethyl-3-(6-dimethyl-4-methylpyridin-3-yl)-7-dipropylaminopyrazolo[l,5-a]pyrimidine), a stressin (CAS RN 170809-51-5), or a photoactivatable analog thereof as described in Bonk et al. "Novel high-affinity photoactivatable antagonists of corticotropin-releasing factor (CRF)" Eur. J. Biochem. 267:3017-3024 (2000), or AAG561 (from Novartis); a melanin concentrating hormone (MCH) antagonist such as 3,5-dimethoxy-N-(1-(naphthalen-2-ylmethyl)piperidin-4-yl)benzamide or (R)-3,5-dimethoxy-N-(1-(naphthalen-2-ylmethyl)-pyrrolidin-3-yl)benzamide (see Kim et al. "Identification of substituted 4-aminopiperidines and 3-aminopyrrolidines as potent MCH-RI antagonists for the treatment of obesity." Bioorg Med Chem Lett. 2006 Jul 29; [electronically published ahead of print] for both), or any MCH antagonist disclosed in U.S. Patent 7,045,636 or published U.S. Patent Application US2005/0171098.

[0099] Further non-limiting examples of antidepressant agents include a tetracyclic compound such as mirtazapine (described, e.g., in U.S. Pat. 4,062,848; see CAS RN 61337-67-5; also known as Remeron, or CAS RN 85650-52-8), mianserin (described, e.g., in U.S. Pat. 3,534,041), or setiptiline.

[0100] Further non-limiting examples of antidepressant agents include agomelatine (CAS RN 1381 12-76-2), pindolol (CAS RN 13523-86-9), antalarmin (CAS RN 157284-96-3), mifepristone (CAS RN 84371-65-3), nemifitide (CAS RN 173240-15-8) or nemifitide ditriflurate (CAS RN 20499-09-6), YKP-IOA or R228060 (CAS RN 561069-23-6),

[0101] Yet additional non-limiting examples of antidepressant agents include CX7 17 from Cortex Pharmaceuticals, TGBAO1AD (a serotonin reuptake inhibitor, 5-HT2 agonist, 5-HTIA agonist, and 5-HT1D agonist) from Fabre-Kramer Pharmaceuticals, Inc., ORG 4420 (an NaSSA (noradrenergic/specific serotonergic antidepressant) from Organon, CP-3 16,3 11 (a CRP1 antagonist) from Pfizer, BMS-562086 (a CRF1 antagonist) from Bristol-Myers Squibb, GW876008 (a CRF1 antagonist) from Neurocrine/GlaxoSmithKline, ONO-2333Ms (a CRF1 antagonist) from Ono Pharmaceutical Co., Ltd., JNJ-19567470 or TS-041 (a CRF1 antagonist) from Janssen (Johnson & Johnson) and Taisho, SSR 125543 or SSR 126374 (a CRF1 antagonist) from Sanofi-Aventis, Lu AA21004 and Lu AA24530 (both from H. Lundbeck AJS), SEP-225289 from Sepracor Inc., ND7001 (a PDE2 inhibitor) from Neuro3d, SSR 4 11298 or SSR 101010 (a fatty acid amide hydrolase, or FAAH, inhibitor) from Sanofi-Aventis, 163090 (a mixed serotonin receptor inhibitor) from GlaxoSmithKline, SSR 241586 (an NK2 and NK3 receptor antagonist) from Sanofi-Aventis, SAR 102279 (an NK2 receptor
antagonist) from Sanofi-Aventis, YKP581 from SK Pharmaceuticals (Johnson & Johnson),
Rl 576 (a GPCR modulator) from Roche, or ND 1251 (a PDE4 inhibitor) from Neuro3d.

Antipsychotic Agents

[0102] In certain embodiments, one or more antipsychotic agents are useful in combination
with a first neurogenic agent of the present invention. Non-limiting examples of antipsychotic
agents as known to the skilled person and useful herein include the following.

[0103] Olanzapine, quetiapine (Seroquel), clozapine (CAS RN 5786-21-0) or its metabolite
ACP-104 (N-desmethylclozapine or norclozapine, CAS RN 6104-71-8), reserpine,
aripiprazole, risperidone, ziprasidone, sertindole, trazodone, paliperidone (CAS RN 144598-
75-4), mifepristone (CAS RN 84371-65-3), bifeprunox or DU-127090 (CAS RN 350992-10-
8), asenapine or ORG 5222 (CAS RN 65576-45-6), iloperidone (CAS RN 133454-47-4),
ocaperidone (CAS RN 129029-23-8), SLV 308 (CAS RN 269718-83-4), licarbazepine or GP
47779 (CAS RN 29331-92-8), Org 34517 (CAS RN 189035-07-2), ORG 34850 (CAS RN
162607-84-3), Org 24448 (CAS RN 211735-76-1), lurasidone (CAS RN 367514-87-2),
blonanserin or lonasen (CAS RN 132810-10-7), Talnetant or SB-223412 (CAS RN 174636-
32-9), secretin (CAS RN 1393-25-5) or human secretin (CAS RN 108153-74-8) which are
endogenous pancreatic hormones, ABT 089 (CAS RN 161417-03-4), SSR 504734 (see
compound 13 in Hashimoto "Glycine Transporter Inhibitors as Therapeutic Agents for
Schizophrenia." Recent Patents on CNS Drug Discovery, 2006 1:43-53), MEM 3454 (see
2006 13(13):1567-84), a phosphodiesterase 10A (PDE10A) inhibitor such as papaverine
(CAS RN 58-74-2) or papaverine hydrochloride (CAS RN 61-25-6), paliperidone (CAS RN
144598-75-4), trifluoperazine (CAS RN 117-89-5), or trifluoperazine hydrochloride (CAS
RN 440-17-5).

[0104] Additional non-limiting examples of antipsychotic agents include trifluoperazine,
fluphenazine, chlorpromazine, perphenazine, thioridazine, haloperidol, loxapine,
mesoridazine, molindone, pimoxide, or thiothixene, SSR 146977 (see Emonds-Alt et al.
"Biochemical and pharmacological activities of SSR 146977, a new potent nonpeptide
tachykinin NK3 receptor antagonist." Can J Physiol Pharmacol, 2002 80(5):482-8),
SSR181507 ([(3-exo)-8-benzoyl-N-[[2 s]7-chloro-2,3-dihydro-1,4-benzodioxin-1-yl]methyl]-
8-azabicyclo[3.2.1]octane-3-methanamine monohydrochloride), or SLV313 (l-(2,3-dihydrobenzo[1,4]dioxin-5-yl)-4-[5-(4-fluorophenyl)-pyridin-3-ylmethyl]-piperazine).

Further non-limiting examples of antipsychotic agents include Lu-35-138 (a D4/5-HT antagonist) from Lundbeck, AVE 1625 (a CBI antagonist) from Sanofi-Aventis, SLV 310,313 (a 5-HT2A antagonist) from Solvay, SSR 181507 (a D2/5-HT2 antagonist) from Sanofi-Aventis, GW07034 (a 5-HT6 antagonist) or GW773812 (a D2, 5-HT antagonist) from GlaxoSmithKline, YKP 1538 from SK Pharmaceuticals, SSR 125047 (a sigma receptor antagonist) from Sanofi-Aventis, MEM 1003 (a L-type calcium channel modulator) from Memory Pharmaceuticals, JNJ-1 7305600 (a GLYT1 inhibitor) from Johnson & Johnson, XY 2401 (a glycine site specific NMDA modulator) from Xytis, PNU 170413 from Pfizer, RGH-188 (a D2, D3 antagonist) from Forrest, SSR 180711 (an alpha7 nicotinic acetylcholine receptor partial agonist) or SSR 103800 (a GLYT1 (Type 1 glycine transporter) inhibitor) or SSR 241586 (a nK3 antagonist) from Sanofi-Aventis.

In other disclosed embodiments, a reported antipsychotic agent may be one used in treating schizophrenia. Non-limiting examples of a reported anti-schizophrenia agent include molindone hydrochloride (MOBAN®) and TC-1827 (see Bohme et al. "In vitro and in vivo characterization of TC-1827, a novel brain α4β2 nicotinic receptor agonist with pro-cognitive activity." Drug Development Research 2004 62(1):26-40).

Agents That Are Thyrotropin-Releasing Hormone (TRH) Receptor Agonists

In certain embodiments, one or more agents comprising a thyrotropin-releasing hormone (TRH) receptor agonist are useful in combination with a first neurogenic agent of the present invention. Non-limiting examples of TRH receptor agonists as known to the skilled person and useful herein include the following.

Non-limiting examples of agents that are agonists of TRH receptor include: thyrotropin-releasing hormone (TRH), N(alpha)-(2-methyl-4-oxocyclopentanecarbonyl)-L-histidyl-L-prolinamide (JTP-2942, CAS Registry No. 148152-77-6), an isomer of JTP-2942, a polymorph of JPT-2942, L-pyro-2-aminoacidipyl-L-leucyl-L-prolinamide (posatirelin, CAS Registry No. 78664-73-0), an isomer of posatirelin, and a polymorph of posatirelin.

The structural formula for JTP-2942 is represented below.
The structural formula for posatirelin is represented below.

Weight Modulating Agents

In certain embodiments, one or more weight modulating agents are useful in combination with a first neurogenic agent of the present invention. Non-limiting examples of weight modulating agents as known to the skilled person and useful herein include the following. These combinations can be used for treating weight gain, metabolic syndrome, or obesity, and/or to induce weight loss.

Non-limiting examples of weigh modulating agents include various diet pills that are commercially or clinically available. In some embodiments, the reported agent for treating weight gain, metabolic syndrome, obesity, or for inducing weight loss is orlistat (CAS RN 96829-58-2), sibutramine (CAS RN 106650-56-0) or sibutramine hydrochloride (CAS RN 84485-00-7), phentermine (CAS RN 122-09-8) or phentermine hydrochloride (CAS RN 1197-21-3), diethylpropion or amfepramone (CAS RN 90-84-6) or diethylpropion hydrochloride, benzphetamine (CAS RN 156-08-1) or benzphetamine hydrochloride, phendimetrazine (CAS RN 634-03-7 or 21784-30-5) or phendimetrazine hydrochloride (CAS RN 17140-98-6) or phendimetrazine tartrate, rimonabant (CAS RN 168273-06-1), bupropion hydrochloride (CAS RN: 31677-93-7), topiramate (CAS RN 97240-79-4), zonisamide (CAS RN 68291-97-4), or APD-356 (CAS RN 846589-98-8).
[0113] In other non-limiting embodiments, the weigh modulating agent may be fenfluramine or Pondimin (CAS RN 458-24-2), dexfenfluramine or Redux (CAS RN 3239-44-9), or levofenfluramine (CAS RN 37577-24-5); or a combination thereof or a combination with phentermine. Non-limiting examples include a combination of fenfluramine and phentermine (or "fen-phen") and of dexfenfluramine and phentermine (or "dextfen-phen").

Agents That Are Antagonist or Inverse Agonist of Opioid Receptors

[0114] In certain embodiments, one or more agents that are antagonists or inverse agonists of at least one opioid receptor are useful in combination with a first neurogenic agent of the present invention. Non-limiting examples of such agents as known to the skilled person and useful herein are described below.

[0115] An opioid receptor antagonist or inverse agonist may be specific or selective (or alternatively non-specific or non-selective) for opioid receptor subtypes. So an antagonist may be non-specific or non-selective such that it antagonizes more than one of the three known opioid receptor subtypes, identified as OP₁, OP₂, and OP₃ (also known as delta, or δ, kappa, or κ, and μ, or μ, respectively). Thus an opioid that antagonizes any two, or all three, of these subtypes, or an inverse agonist that is specific or selective for any two or all three of these subtypes, may be used as the neurogenic agent in the practice of certain embodiments. Alternatively, an antagonist or inverse agonist may be specific or selective for one of the three subtypes, such as the kappa subtype as a non-limiting example.

[0116] Non-limiting examples of reported opioid antagonists include naltrexind, naloxone, naloxene, naltrexone, JDTic (Registry Number 785835-79-2; also known as 3-isoquinolinecarboxamide, 1,2,3,4-tetrahydro-7-hydroxy-N-[(1S)-1-[(3R,4R)-4-(3-hydroxyphenyl)-3,4-dimethyl-1-piperidinyl]methyl]-2-methylpropyl]-dihydrochloride, (3R)-(9Cl)), nor-binaltorphimine, and buprenorphine. In some embodiments, a reported selective kappa opioid receptor antagonist compound, as described in US 2002/0132828, U.S. Patent 6,559,159, and/or WO 2002/053533, may be used. Further non-limiting examples of such reported antagonists is a compound disclosed in U.S. Patent 6,900,228, arodyn (Ac[Ph(1,2,3),Arg(4),d-Ala(8)]Dyn A-(I-1 1)NH(2), as described in Bennett, et al. (2002) J. Med. Chem. 45:5617-5619), and an active analog of arodyn as described in Bennett e al. (2005) J Pept Res. 65(3):322-32, alvimopan.
In some embodiments, the neurogenic agent used in the methods described herein has "selective" activity (such as in the case of an antagonist or inverse agonist) under certain conditions against one or more opioid receptor subtypes with respect to the degree and/or nature of activity against one or more other opioid receptor subtypes. For example, in some embodiments, the neurogenic agent has an antagonist effect against one or more subtypes, and a much weaker effect or substantially no effect against other subtypes. As another example, an additional neurogenic agent used in the methods described in certain embodiments herein may act as an agonist at one or more opioid receptor subtypes and as antagonist at one or more other opioid receptor subtypes. In some embodiments, a neurogenic agent has activity against kappa opioid receptors, while having substantially lesser activity against one or both of the delta and mu receptor subtypes. In other embodiments, a neurogenic agent has activity against two opioid receptor subtypes, such as the kappa and delta subtypes. As non-limiting examples, the agents naloxone and naltrexone have nonselective antagonist activities against more than one opioid receptor subtypes. In certain embodiments, selective activity of one or more opioid antagonists results in enhanced efficacy, fewer side effects, lower effective dosages, less frequent dosing, or other desirable attributes.

An opioid receptor antagonist is an agent able to inhibit one or more characteristic responses of an opioid receptor or receptor subtype. As a non-limiting example, an antagonist may competitively or non-competitively bind to an opioid receptor, an agonist or partial agonist (or other ligand) of a receptor, and/or a downstream signaling molecule to inhibit a receptor's function.

An inverse agonist able to block or inhibit a constitutive activity of an opioid receptor may also be used in certain embodiments. An inverse agonist may competitively or non-competitively bind to an opioid receptor and/or a downstream signaling molecule to inhibit a receptor's function. Non-limiting examples of inverse agonists include ICI-174864 (N,N-diallyl-Tyr-Aib-Aib-Phe-Leu), RTI-5989-1, RTI-5989-23, and RTI-5989-25 (see Zaki et al. J. Pharmacol. Exp. Therap. 298(3): 1015-1020, 2001).

Androgen Receptor Modulating Agents

In certain embodiments, one or more androgen receptor modulating agents are useful in combination with a first neurogenic agent of the present invention. Non-limiting
Examples of such agents as known to the skilled person and useful herein include the androgen receptor agonists hydroepiandrosterone (DHEA) and DHEA sulfate (DHEAS).

**Agents That Inhibit Rho Kinase**

In certain embodiments, one or more Rho kinase inhibiting agents are useful in combination with a first neurogenic agent of the present invention. Non-limiting examples of agents that inhibit Rho kinase as known to the skilled person and useful herein include the following.

In certain non-limiting embodiments, the Rho kinase inhibiting agents include fasudil (CAS RN 103745-39-7); fasudil hydrochloride (CAS RN 105628-07-7); the metabolite of fasudil, which is hydroxyfasudil (see Shimokawa et al. "Rho-kinase-mediated pathway induces enhanced myosin light chain phosphorylations in a swine model of coronary artery spasm." Cardiovasc Res. 1999 43:1029-1039), Y 27632 (CAS RN 138381-45-0); a fasudil analog thereof such as (S)-Hexahydro-1-(4-ethenylisoquinoline-5-sulfonyl)-2-methyl-1H-1,4-diazepine, (S)-hexahydro-4-glycyl-2-methyl-1-(4-methylisoquinoline-5-sulfonyl)-1H-1,4-diazepine, or (S)-(+)-2-methyl-1-[(4-methyl-5-isoquinoline)sulfonyl]-homopiperazine (also known as H-1152P; see Sasaki et al. "The novel and specific Rho-kinase inhibitor (S)-(+)-2-methyl-1-[(4-methyl-5-isoquinoline)sulfonyl]-homopiperazine as a probing molecule for Rho-kinase-involved pathway." Pharmacol Ther. 2002 93(2-3):225-32); or a substituted isoquinolinesulfonamide compound as disclosed in U.S. Patent 6,906,061.

**Agents That Inhibit or Modulate GSK-3**

In certain embodiments, one or more agents that inhibit or modulate GSK-3 are useful in combination with a first neurogenic agent of the present invention. Non-limiting examples of such agents as known to the skilled person and useful herein include the following.

In certain non-limiting embodiments, the GSK3-beta modulator is a paullone, such as alsterpaullone, kenpaullone (9-bromo-7,12-dihydropindolo[3,2-d]benzazepin-6(5H)-one), gwennpaullone (see Knockaert et al. "Intracellular Targets of Paullones. Identification following affinity purification on immobilized inhibitor." J Biol Chem. 2002 277(28):25493-501), azakenpaullone (see Kunick et al. "1-Azakenpaullone is a selective inhibitor of glycogen synthase kinase-3 beta." Bioorg Med Chem Lett. 2004 14(2):413-6), or the

Glutamate Modulating Agents and mGlu Receptor Modulating Agents

In certain embodiments, one or more glutamate modulating or metabotropic glutamate (mGlu) receptor modulating agents are useful in combination with a first neurogenic agent of the present invention. Non-limiting examples of such agents as known to the skilled person and useful herein include the following.

In some embodiments, the reported mGlu receptor modulator is a Group II modulator, having activity against one or more Group II receptors (mGlu$_2$ and/or mGlu$_3$).

Embodiments include those where the Group II modulator is a Group II agonist. Non-limiting examples of Group II agonists include: (i) (LS,3R)-1-aminocyclopentane-1,3-dicarboxylic acid (ACPD), a broad spectrum mGlu agonist having substantial activity at Group I and II receptors; (ii) (-)-2-thia-4-aminobicyclo-hexane-4,6-dicarboxylate (LY389795), which is

[0127] Non-limiting examples of reported Group II antagonists include: (i) phenylglycine analogues, such as (RS)-alpha-methyl-4-sulphonophenylglycine (MSPG), (RS)-alpha-methyl-4-phosphonophenylglycine (MPPG), and (RS)-alpha-methyl-4-tetrazolylphenylglycine (MTPG), described in Jane et al., Neuropharmacology 34: 851-856 (1995); (ii) LY366457, which is described in O’Neill et al., Neuropharmacol., 45(5): 565-74 (2003); (iii) compounds described in US App Nos. 20050049243, 200501 19345 and 20030157647; and (iv) the Group II-specific modulators described below.

[0128] In some non-limiting embodiments, the reported Group II modulator is a Group II-selective modulator, capable of modulating mGlur2 and/or mGlur3 under conditions where it is substantially inactive at other mGlur subtypes (of Groups I and III). Examples of Group II-selective modulators include compounds described in Monn, et al., J. Med. Chem., 40, 528-537 (1997); Schoepp, et al., Neuropharmacol., 36, 1-1 1 (1997) (e.g., IS,2S,5R,6S-2-aminobicyclohexane-2,6-dicarboxylate); and Schoepp, Neurochem. Int., 24, 439 (1994).

[0129] Non-limiting examples of reported Group II-selective agonists include (i) (+)-2-aminobicyclohexane-2,6-dicarboxylic acid (LY354740), which is described in Johnson et al., Drug Metab. Disposition, 30(1): 27-33 (2002) and Bond et al., NeuroReport 8: 1463-1466 (1997), and is systemically active after oral administration (e.g., Grillon et al., Psychopharmacol. (Berl), 168: 446-454 (2003)); (ii) (-)-2-Oxa-4-aminobicyclohexane-4,6-dicarboxylic acid (LY379268), which is described in Monn et al., J. Med. Chem. 42: 1027-1040 (1999) and US Pat. No. 5,688,826. LY379268 is readily permeable across the blood-brain barrier, and has EC50 values in the low nanomolar range (e.g., below about 10 nM, or below about 5 nM) against human mGlur2 and mGlur3 receptors in vitro; (iii) (2R,4R)-4-aminopyrrolidine-2,4-dicarboxylate ((2R,4R)-APDC), which is described in Monn et al., J. Med. Chem. 39: 2990 (1996) and Schoepp et al., Neuropharmacology, 38: 1431 (1999); (iv) (IS,3S)-1-aminocyclopentane-1,3-dicarboxylic acid ((IS,3S)-ACPD), described in Schoepp, Neurochem. Int., 24: 439 (1994); (v) (2i?,4i?)′-4-aminopyrrolidine-2,4-dicarboxylic acid ((2R,4R)-APDC), described in Howson and Jane, British Journal of Pharmacology, 139, 147-155 (2003); (vi) (2S,′i?,2S′)-2-(carboxycyclopropyl)-glycine (L-CCG-I), described in Brabet et al., Neuropharmacology 37: 1043-1051 (1998); (vii) (2S,2′R,3′R)-2-(2′,3′-

[0130] Non-limiting examples of reported Group II-selective antagonists useful in methods provided herein include the competitive antagonist (2S)-2-amino-2-(2’-carboxy-3’-phenylcyclopropyl)glycine (APICA), which is described, e.g., in Kingston et al., Neuropharmacology 37: 1-12 (1998) and Monn et al., J Med Chem 42: 1027-1040 (1999). LY341495 is readily permeably across the blood-brain barrier, and has IC\textsubscript{50} values in the low nanomolar range (e.g., below about 10 nM, or below about 5 nM) against cloned human mGlu\textsubscript{2} and mGlu\textsubscript{3} receptors. LY341495 has a high degree of selectivity for Group II receptors relative to Group I and Group III receptors at low concentrations (e.g., nanomolar range), whereas at higher concentrations (e.g., above 1\mu M), LY341495 also has antagonist activity against mGlu\textsubscript{7} and mGlu\textsubscript{8}, in addition to mGlu\textsubscript{2/3}. LY341495 is substantially inactive against KA, AMPA, and NMDA iGlu receptors.

[0131] Additional non-limiting examples of reported Group II-selective antagonists include the following compounds, indicated by chemical name and/or described in the cited references: (i) \kappa-methyl-L-(carboxycyclopropyl) glycine (CCG); (ii) (2S,3S,4S)-2-amino-3-(3,4-dichlorobenzyloxy)-6 fluorobicyclohexane-2,6-dicarboxylic acid (MGS0039), which is described in Nakazato et al., J. Med. Chem., 47(18):4570-87 (2004); (iv) an n-hexyl, n-heptyl, n-octyl, 5-methylbutyl, or 6-methylpenty1 ester prodrug of MGS0039; (v) MGS0210 (3-(3,4-dichlorobenzyloxy)-2-amino-6-fluorobicyclohexane-2,6-dicarboxylic acid n-heptyl ester); (vi) (RS)-1-amino-5-phosphonoindan-l-carboxy1ic acid (APICA), which is described in Ma et al., Bioorg. Med. Chem. Lett., 7: 1195 (1997); (vii) (25)-ethylglutamic acid (EGLU), which is described in Thomas et al., Br. J. Pharmacol., 117: 70P (1996); (viii) (2S,1’S,2’S,3’R)-2-(2’-carboxy-3’-phenylcyclopropyl)glycine (PCCG-IV); and (ix) compounds described in US Pat No. 6,107,342 and US App No. 2004000614. APICA has an IC\textsubscript{50} value of approximately 30 \mu M against mGluR\textsubscript{2} and mGluR\textsubscript{3}, with no appreciable activity against Group I or Group III receptors at sub-mM concentrations.
In some non-limiting embodiments, a reported Group II-selective modulator is a subtype-selective modulator, capable of modulating the activity of mGlu₂ under conditions in which it is substantially inactive at mGlu₃ (mGlu₂-selective), or vice versa (mGlu₃-selective). Non-limiting examples of subtype-selective modulators include compounds described in US Pat Nos. 6,376,532 (mGlu₂-selective agonists) and US App No. 20040002478 (mGlu₃-selective agonists). Additional non-limiting examples of subtype-selective modulators include allosteric mGlu receptor modulators (mGlu₂ and mGlu₃) and NAAG-related compounds (mGlu₃), such as those described below.

In other non-limiting embodiments, a reported Group II modulator is a compound with activity at Group I and/or Group III receptors, in addition to Group II receptors, while having selectivity with respect to one or more mGlu receptor subtypes. Non-limiting examples of such compounds include: (i) (2S,35,45)-2-(carboxycyclopropyl)glycine (L-CCG-I) (Group I/Group II agonist), which is described in Nicoletti et al., Trends Neurosci., 19: 267-271 (1996), Nakagawa, et al., Eur. J. Pharmacol., 184, 205 (1990), Hayashi, et al., Br. J. Pharmacol., 107, 539 (1992), and Schoepp et al., J. Neurochem., 63., page 769-772 (1994); (ii) (S)-4-carboxy-3-hydroxyphenylglycine (4C₃,HPG) (Group II agonist/Group I competitive antagonist); (iii) gamma-carboxy-L-glutamic acid (GLA) (Group II antagonist/Group III partial agonist/antagonist); (iv) (2S,2'R,3'R)-2-(2,3-dicarboxycyclopropyl)glycine (DCG-IV) (Group II agonist/Group III antagonist), which is described in Ohfune et al, Bioorg. Med. Chem. Lett., 3: 15 (1993); (v) (RS)-a-methyl-4-carboxyphenylglycine (MCPG) (Group I/Group II competitive antagonist), which is described in Eaton et al., Eur. J. Pharmacol., 244: 195 (1993), Collingridge and Watkins, TiPS, 15: 333 (1994), and Joly et al., J. Neurosci., 15: 3970 (1995); and (vi) the Group II/III modulators described in US Pat Nos. 5,916,920, 5,688,826, 5,945,417, 5,958,960, 6,143,783, 6,268,507, 6,284,785.

In some non-limiting embodiments, the reported mGlu receptor modulator comprises (S)-MCPG (the active isomer of the Group I/Group II competitive antagonist (RS)-MCPG) substantially free from (R)-MCPG. (S)-MCPG is described, e.g., in Sekiyama et al., Br. J. Pharmacol., 117: 1493 (1996) and Collingridge and Watkins, JjPS, 15: 333 (1994).

Additional non-limiting examples of reported mGlu modulators useful in methods disclosed herein include compounds described in US Pat Nos. 6,956,049, 6,825,211, 5,473,077, 5,912,248, 6,054,448, and 5,500,420; US App Nos. 20040077599, 20040147482,

[0136] In some non-limiting embodiments, the reported mGlu receptor modulator is a prodrug, metabolite, or other derivative of N-Acetylaspartylglutamate (NAAG), a peptide neurotransmitter in the mammalian CNS that is a highly selective agonist for mGluR₃ receptors, as described in Wroblewska et al., J. Neurochem., 69(1): 174-181 (1997). In other embodiments, the mGlu modulator is a compound that moduates the levels of endogenous NAAG, such as an inhibitor of the enzyme N-acetylated-alpha-linked-acidic dipeptidase (NAALADase), which catalyzes the hydrolysis of NAAG to N-acetyl-aspartate and glutamate. Examples of NAALADase inhibitors include 2-PMPA (2-(phosphonomethyl)pentanedioic acid), which is described in Slusher et al., Nat. Med., 5(12): 1396-402 (1999); and compounds described in J. Med. Chem., 39: 619 (1996), US Pub. No. 20040002478, and US Pat Nos. 6,313,159, 6,479,470, and 6,528,499. In some embodiments, the mGlu modulator is the mGlu₃-selective antagonist, beta-NAAG.

[0137] Additional non-limiting examples of reported glutamate modulators include memantine (CAS RN 19982-08-2), memantine hydrochloride (CAS RN 41100-52-1), and riluzole (CAS RN 1744-22-5).

[0138] In some non-limiting embodiments, a reported Group II modulator is administered in combination with one or more additional compounds reported as active against a Group I and/or a Group III mGlu receptor. For example, in some cases, methods comprise modulating the activity of at least one Group I receptor and at least one Group II mGlu receptor (e.g., with a compound described herein). Examples of compounds useful in modulating the activity of Group I receptors include Group I-selective agonists, such as (i) trans-azetidine-2,4-dicarboxylic acid (tADA), which is described in Kozikowski et al., J. Med. Chem., 36: 2706 (1993) and Manahan-Vaughan et al., Neuroscience, 72: 999 (1996); (ii) (RS)-3,5-Dihydroxyphenylglycine (DHPG), which is described in Ito et al., NeuroReport, 3: 1013 (1992); or a composition comprising (S)-DHPG substantially free of (R)-DHPG, as described, e.g., in Baker et al., Bioorg. Med. Chem. Lett., 5: 223 (1995); (iii) (RS)-3-Hydroxyphenylglycine, which is described in Birse et al., Neuroscience, 52: 481 (1993); or a composition comprising (S)-3-Hydroxyphenylglycine substantially free of (R)-3-Hydroxyphenylglycine, as described, e.g., in Hayashi et al., J. Neuroscience, 14: 3370 (1994); (iv)
and (S)-Homoquisqualate, which is described in Porter et al., Br. J. Pharmacol., 106: 509 (1992).

[0139] Additional non-limiting examples of reported Group I modulators include (i) Group I agonists, such as (RS)-3,5-dihydroxyphenylglycine, described in Brabet et al., Neuropharmacology, 34, 895-903, 1995; and compounds described in US Pat Nos. 6,399,641 and 6,589,978, and US Pub No. 20030212066; (ii) Group I antagonists, such as (S)-4-Carboxy-3-hydroxyphenylglycine; 7-(Hydroxyimino)cyclopropa-β-chromen-1α-carboxylate ethyl ester; (RS)-l-Aminoisindan-l,5-dicarboxylic acid (AIDA); 2-Methyl-6-(phenylethynyl)pyridine (MPEP); 2-Methyl-6-(2-phenylethenyl)pyridine (SIB-1893); 6-Methyl-2-(phenylazo)-3-pyridinol (SIB-1757); (RS)-2-Chloro-5-hydroxyphenylglycine (CHPG); and (iv) mGlu₅-selective antagonists, such as 2-methyl-6-(phenylethynyl)-pyridine (MPEP); and compounds described in US Pat No. 6,660,753; and US Pub Nos. 20030195139, 20040229917, 20050153986, 20050085514, 20050065340, 20050026963, 20050020585, and 20040259917.

[0140] Non-limiting examples of compounds reported to modulate Group III receptors include (i) the Group III-selective agonists (L)-2-amino-4-phosphonobutyric acid (L-AP4), described in Knopfel et al., J. Med Chem., 38, 1417-1426 (1995); and (S)-2-Amino-2-methyl-4-phosphonobutanoic acid; (ii) the Group III-selective antagonists (RS)-α-Cyclopropyl-4-phosphonophenylglycine; (RS)-α-Methylserine-O-phosphate (MSOP); and compounds described in US App. No. 20030109504; and (iii) (JS,3R,4S)-1-aminocyclopentane-1,2,4-tricarboxylic acid (ACPT-I).

AMPA Modulating Agents

[0141] In certain embodiments, one or more AMPA modulating agents are useful in combination with a first neurogenic agent of the present invention. AMPA is a specific agonist of the AMPA type of glutamate receptors and has the chemical formula: alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid. Non-limiting examples of AMPA modulating agents (including AMPA type glutamate receptor sensitizers) as known to the skilled person and useful herein include the following.
CX-516 or ampalex (CAS RN 154235-83-3), Org-24448 (CAS RN 211735-76-1), LY451395 (2-propanesulfonamide, N-[(2R)-2-[4'-(methylsulfonyl)amino]ethyl] [1,1'-biphenyl]-4-yl]propyl-), LY-450108 (see Jhee et al. "Multiple-dose plasma pharmacokinetic and safety study of LY450108 and LY451395 (AMPA receptor potentiators) and their concentration in cerebrospinal fluid in healthy human subjects." J Clin Pharmacol. 2006 46(4):424-32), and CX717. Additional examples of reported antagonists include irampanel (CAS RN 206260-33-5) and E-2007.

Further non-limiting examples of reported AMPA receptor antagonists for use in combinations include YM90K (CAS RN 154164-30-4), YM872 or Zonampanel (CAS RN 210245-80-0), NBQX (or 2,3-Dioxo-6-nitro-7-sulfamoylbenzo(f)quinoxaline; CAS RN 118876-58-7), PNQX (1,4,7,8,9,10-hexahydro-9-methyl-6-nitropyrido[3,4-f]quinoxaline-2,3-dione), and ZK200775 ([1,2,3,4-tetrahydro-7-morpholinyl-2,3-dioxo-6-(fluoromethyl) quinoxalin-1-yl] methylphosphonate).

Still further non-limiting examples of AMPA modulators include CX-516 or ampalex (CAS RN 154235-83-3), Org-24448 (CAS RN 211735-76-1), LY451395 (2-propanesulfonamide, N-[(2R)-2-[4'-(methylsulfonyl)amino]ethyl] [1,1'-biphenyl]-4-yl]propyl-), LY-450108 (see Jhee et al. "Multiple-dose plasma pharmacokinetic and safety study of LY450108 and LY451395 (AMPA receptor potentiators) and their concentration in cerebrospinal fluid in healthy human subjects." J Clin Pharmacol. 2006 46(4):424-32), and CX717. Additional examples of reported antagonists include irampanel (CAS RN 206260-33-5) and E-2007.

**Muscarinic Agents**

In certain embodiments, one or more muscarinic agents, preferably agonists, are useful in combination with a first neurogenic agent of the present invention. Non-limiting examples of muscarinic agents as known to the skilled person and useful herein include the following.

The muscarinic agonist milameline (CI-979), or a compound that is structurally or functionally related to milameline. Structures, biological activity data, methods for obtaining biological activity data, methods of synthesis, modes of administration and pharmaceutical formulations for milameline and related compounds are disclosed in U.S. Patent Nos. 4,786,648, 5,362,860, 5,424,301, 5,650,174, 4,710,508, 5,314,901, 5,356,914, and 5,356,912.
In other embodiments, the muscarinic agonist is xanomeline, or a compound that is structurally or functionally related to xanomeline. Structures, biological activity data, methods for obtaining biological activity data, methods of synthesis, modes of administration and pharmaceutical formulations for xanomeline and related compounds are disclosed in U.S. Patent Nos. 5,041,455, 5,043,345, and 5,260,314.

In further embodiments, the muscarinic agent is alvameline (LU 25-109), or a compound that is functionally or structurally related to alvameline. Structures, biological activity data, methods for obtaining biological activity data, methods of synthesis, modes of administration and pharmaceutical formulations for alvameline and related compounds are disclosed in U.S. Pat. Nos. 6,297,262, 4,866,077, RE36,374, 4,925,858, PCT Publication No. WO 97/17074, and in Moltzen et al, J Med Chem. 1994 Nov 25;37(24):4085-99.

In additional embodiments, the muscarinic agent is 2,8-dimethyl-3-methylene-1-oxa-8-azaspiro[4.5]decane (YM-796) or YM-954, or a functionally or structurally related compound. Structures, biological activity data, methods for obtaining biological activity data, methods of synthesis, modes of administration and pharmaceutical formulations for YM-796, YM-954, and related compounds are disclosed in U.S. Patent Nos. 4,940,795, RE34,653, 4,996,210, 5,041,549, 5,403,931, and 5,412,096, and in Wanibuchi et al., Eur. J. Pharmacol., 187, 479-486 (1990).

In yet further embodiments, the muscarinic agent is cevimeline (AF1 02B) or a compound that is functionally or structurally related to cevimeline. Cevimeline is approved by the FDA for the treatment of symptoms of dry mouth in patients with Sjogren's Syndrome. Structures, biological activity data, methods for obtaining biological activity data, methods of synthesis, modes of administration and pharmaceutical formulations for cevimeline and related compounds are disclosed in U.S. Pat. Nos. 4,855,290, 5,340,821, 5,580,880 (American Home Products), and 4,981,858 (optical isomers of AF102B).

In yet additional embodiments, the muscarinic agent is sabcomeline (SB 202026), or a compound that is functionally or structurally related to sabcomeline. Structures, biological activity data, methods for obtaining biological activity data, methods of synthesis, modes of administration and pharmaceutical formulations for sabcomeline and related compounds are described in U.S. Patent Nos. 5,278,170, RE35,593, 6,468,560, 5,773,619, 5,808,075, 5,545,740, 5,534,522, and 6,596,869, U.S. Patent Publication Nos. 2002/0127271, 2003/0129246, 2002/0150618, 2001/0018074, 2003/0157169, and 2001/0003588, Bromidge


[0153] In some embodiments, the muscarinic agent is a 1-methyl-1,2,5,6-tetrahydropyridyl-1,2,5-thiadiazole derivative, such as tetra(ethyleneglycol)(4-methoxy-1,2,5-thiadiazol-3-yl)[3-(1-methyl-1,2,5,6-tetrahydropyrid-3-yl)-1,2,5-thiadiazol-4-yl]ether, or a compound that is functionally or structurally related to a 1-methyl-1,2,5,6-tetrahydropyridyl-1,2,5-thiadiazole derivative. Structures, biological activity data, methods for obtaining biological activity data, methods of synthesis, and other information relating to using these derivatives and related compounds as pharmaceutical agents is provided by Cao et al. ("Synthesis and biological characterization of 1-methyl-1,2,5,6-tetrahydropyridyl-1,2,5-thiadiazole derivatives as muscarinic agonists for the treatment of neurological disorders." J. Med. Chem. 46(20):4273-4286, 2003).

[0154] In further embodiments, the muscarinic agent is besipiridine, SR-46559, L-689,660, S-9977-2, AF-102, or thiopilocarpine. The structures, biological activity data, methods for obtaining biological activity data, methods of synthesis, modes of administration and pharmaceutical formulations for these and related compounds are known in the art and/or described in the publications referenced herein.

[0155] In yet further embodiments, the muscarinic agent is an analog of clozapine or a pharmaceutically acceptable salt, ester, amide, or prodrug form thereof. In some embodiments, the analog is a diaryl[a,d]cycloheptene, such as an amino substituted form thereof. A compound that is functionally or structurally related to such analogs of clozapine may also be used in the practice of the invention. In some embodiments, the compound is N-desmethyclozapine, which has been reported to be a metabolite of clozapine and discovered to be highly neurogenic in assays as disclosed herein. Structures, biological activity data, methods for obtaining biological activity data, methods of synthesis, modes of administration
and pharmaceutical formulations for these analogs and related compounds are disclosed in US 2005/0192268 and WO 05/63254.

[0156] In other embodiments, the muscarinic agent is a muscarinic receptor agonist selected from 55-LH-3B, 55-LH-25A, 55-LH-30B, 55-LH-4-1A, 40-LH-67, 55-LH-15A, 55-LH-16B, 55-LH-1 1C, 55-LH-31A, 55-LH-46, 55-LH-47, 55-LH-4-3A, or a compound that is functionally or structurally related to one or more of these agonists. Structures, biological activity data, methods for obtaining biological activity data, methods of synthesis, modes of administration and pharmaceutical formulations for these agonists and related compounds are disclosed in US 2005/0130961 and WO 04/087158.

[0157] In additional embodiments, the muscarinic agent is a benzimidazolidinone derivative or a compound that is functionally or structurally related to a benzimidazolidinone derivative. The derivative or related compound may be selective for the m1 and/or In2 receptor subtypes. Structures, biological activity data, methods for obtaining biological activity data, methods of synthesis, modes of administration and pharmaceutical formulations for these derivatives and related compounds are disclosed in U.S. Patent 6,951,849, US 2003/0100545, WO 04/089942, and WO 03/028650.

[0158] In yet additional embodiments, the muscarinic agent is a spiroazacyclic compound or a compound that is functionally or structurally related to a spiroazacyclic compound. In some embodiments, the compound is 1-oxa-3,8-diaza-spiro[4,5]decan-2-one. Structures, biological activity data, methods for obtaining biological activity data, methods of synthesis, modes of administration and pharmaceutical formulations for these spiroazacyclic compounds and related compounds are disclosed in U.S. Patent 6,911,452 and WO 03/057698.

[0159] In other embodiments, the muscarinic agent is a tetrahydroquinoline analog or a compound that is functionally or structurally related to a tetrahydroquinoline analog. Structures, biological activity data, methods for obtaining biological activity data, methods of synthesis, modes of administration and pharmaceutical formulations for these spiroazacyclic compounds and related compounds are disclosed in US 2003/0176418, US 2005/0209226, and WO 03/057672.

[0160] In further embodiments, the agent is a muscarinic agonist or a compound that is functionally or structurally related to such an agonist. Structures, biological activity data, methods for obtaining biological activity data, methods of synthesis, modes of administration
and pharmaceutical formulations for these agonists and related compounds are disclosed in U.S. Patent 6,627,645, US 2005/01 13357, and WO 01/83472.

[0161] In yet further embodiments, the agent is a muscarinic agonist or a compound that is functionally or structurally related to such an agonist. Structures, biological activity data, methods for obtaining biological activity data, methods of synthesis, modes of administration and pharmaceutical formulations for these agonists and related compounds are disclosed in U.S. Patents 6,528,529, US 2003/0144285, WO 01/05763, and WO 99/50247.


**Acetylcholinesterase Inhibitors**

[0163] In certain embodiments, one or more acetylcholinesterase (AChE) inhibitors are useful in combination with a first neurogenic agent of the present invention. Non-limiting examples of AChE inhibitors as known to the skilled person and useful herein include the following.

[0164] AChE inhibitors, like metrifonate or echothiophate. Metrifonate is also known as metriphonate or trichlorfon or its active metabolite, 2,2-dimethylchlorovinyl phosphate (or dichlorvos or DDVP). Metrifonate is represented by the following formula:

\[(\text{CH}_3\text{O})_2\text{PO-CHOH-OCl}_3\].
Metrifonate has been used to treat Alzheimer's Disease (see the studies of Cummings et al. "The efficacy of Metrifonate in improving the behavioral disturbance of Alzheimer's disease patients." Neurology 1998; 50:A251).

Echothiophate is also known as ecothioptate, echothiophate iodide, phospholine iodide, (2-Mercaptoethyl)trimethylammonium S-ester with O,O'-diethylphosphorothioate, BRN 1794025, ecothiopatum, or phospholine. Echothiophate is referenced by CAS Registry Number 6736-03-4.

In other embodiments, an AChE inhibitor is an aminoacridine such as tacrine or ipidacrine as non-limiting examples. Tacrine is also known as tetrahydroaminoacridine or THA. Tacrine is referenced by CAS Registry Number 321-64-2. Ipidacrine is also known as Amiridin.

In additional embodiments, an AChE inhibitor is a carbamate such as physostigmine, neostigmine, or rivastigmine as non-limiting examples.

Physostigmine, also known as 1,2,3,3a,8,8a-hexahydro-1,3a,8-trimethyl-, methylcarbamate (ester) or (3aS,8aR)-pyrrolo(2,3-b)indol-5-ol, is referenced by CAS number 57-47-6. It is a tertiary amine capable of crossing the blood-brain barrier.

Neostigmine, or m-hydroxyphenyl)trimethyl-dimethylcarbamate(ester) ammonium, is referenced by CAS number 59-99-4.

Rivastigmine is also known as rivastigmine tartrate or (S)-N-Ethyl-N-methyl-3-[l-(dimethylamino)ethyl] -phenyl carbamate hydrogen-(2R,3R)-tartrate or SDZ ENA 713 or ENA 713. The reference for rivastigmine is CAS Registry Number 123441-03-2.

In further embodiments, an AChE inhibitor is a carbamate phenanthrine derivative such as galantamine or its hydrogen bromide form as non-limiting examples.

Galantamine is also known as (4aS,6R,8aS)-4a,5,9,10,1 1,12-hexahydro-3-methoxy-11-methyl-6H-benzofuro(3a,3,2-ef)(2)benzazepin-6-ol and is often used in its hydrogen bromide form. Galantamine is referenced by CAS number 357-70-0.

An AChE inhibitor may also be a piperidine derivative, such as donepezil as a non-limiting example. Donepezil is also known as 2,3-dihydro-5,6-dimethoxy-2-((1-(phenylmethyl)-4-piperidinyl)methyl)-IH-inden-1-one, and is referenced by CAS number 120014-06-4.
Itopride may also be an AChE inhibitor for use in embodiments disclosed herein. Itopride HCl is referenced by CAS Registry Number 122898-67-3. In one embodiment, a total daily dose range for itopride HCl is from about 25 mg to about 1000 mg, or between about 100 mg to about 300 mg. In some embodiments, the AChE inhibitor, or neurogenic agent, is the IV-oxide derivative of itopride, which is the primary human metabolite of itopride HCl.

Another AChE inhibitor for use in the disclosed embodiments is (-)-huperzine A, which is also referred to as HupA and 1-amino-13-ethylidene-l 1-methyl-6-aza-tricyclo[7.3.1.02,7]trideca-2(7),3,10-trien-5-one. It is referenced by CAS number 102518-79-6.

A further embodiment of an AChE inhibitor is phenserine, the structure and synthesis of which is described in U.S. Patent 6,495,700.

**Folates and One-Carbon Metabolism Modulators**

In certain embodiments, factors involved in one-carbon metabolism such as folic acid and/or one or more folic acid derivatives, are useful in combination with a first neurogenic agent of the present invention. Non-limiting examples of folic acid derivatives as known to the skilled person and useful herein include folates, methylfolate, and L-methylfolate.

**HDAC Antagonist Agents**

In certain embodiments, one or more HDAC inhibitory agents are useful in combination with a first neurogenic agent of the present invention. Non-limiting examples of HDAC agents as known to the skilled person and useful herein include the following.

The term "HDAC" refers to any one of a family of enzymes that remove acetyl groups from the epsilon-amino groups of lysine residues at the N-terminus of a histone. An HDAC inhibitor refers to compounds capable of inhibiting, reducing, or otherwise modulating the deacetylation of histones mediated by a histone deacetylase. Non-limiting examples of a reported HDAC inhibitor include a short-chain fatty acid, such as butyric acid, phenylbutyrate (PB), 4-phenylbutyrate (4-PBA), pivaloyloxymethyl butyrate (Pivanex, AN-9), isovalerate, valerate, valproate, valproic acid, propionate, butyramide, isobutyramide, phenylacetate, 3-bromopropionate, or tributyrin; a compound bearing a hydroxyamic acid
group, such as suberoylanide hydroxamic acid (SAHA), trichostatin A (TSA), trichostatin C (TSC), salicyldihydroxamic acid, oxamflatin, suberic bis-hydroxamic acid (SBHA), m-carboxy-
cinnamic acid bis-hydroxamic acid (CBHA), pyroxamide (CAS RN 382180-17-8), diethyl bis-
(pentamethylene-N,N-dimethylcarboxamide) malonate (EMBA), azelaic bis-hydroxamic acid
(ABHA), azelaic-1-hydroxamate-9-anilide (AAHA), 6-(3-Chlorophenylureido) carpoic
hydroxamic acid, or A-1 61906; a cyclic tetrapeptide, such as Depsipeptide (FK228),
FR225497, trapoxin A, apicidin, chlamydocin, or HC-toxin; a benzamide, such as MS-275;
depudecin, a sulfonamide anilide (e.g., diallyl sulfide), BL1521, curcumin
diferuloylmethane), CI-994 (N-acetyldinaline), spiruchostatin A, Scriptaid, carbamazepine
(CBZ), or a related compound; a compound comprising a cyclic tetrapeptide group and a
hydroxamic acid group (examples of such compounds are described in U.S. Patent Nos.
6,833,384 and 6,552,065); a compound comprising a benzamide group and a hydroxamic
acid group (examples of such compounds are described in Ryu et al., Cancer Lett. 2005 Jul 9
(electronically published), Plumb et al., Mol Cancer Ther., 2(8):721-8 (2003), Ragno et al., J
(2005), and Mai et al., J Med Chem., 46(23):4826-9 (2003)); a compound described in U.S.
Patent Nos. 6,897,220, 6,888,027, 5,369,108, 6,541,661, 6,720,445, 6,562,995, 6,777,217, or
6,387,673, or U.S. Patent Publication Nos. 2005/0171347, 2005/0165016, 2005/0159470,
2005/0143385, 2005/0137234, 2005/0137232, 2005/01 19250, 2005/01 13373, 2005/0107445,
2002/01 19996, 2002/01 15826, 2002/0103192, or 2002/0065282; FK228, AN-9, MS-275, CI-
994, SAHA, G2M-777, PXD-101, LBH-589, MGCD-0103, MK0683, sodium
phenylbutyrate, CRA-02478 1, and derivatives, salts, metabolites, prodrugs, and stereoisomers
thereof; and a molecule that inhibits the transcription and/or translation of one or more
HDACs.

[0181] Additional non-limiting examples include a reported HDAC inhibitor selected from
ONO-2506 or arundic acid (CAS RN 185517-21-9); MGCD0103 (see Gelmon et al. "Phase I
trials of the oral histone deacetylase (HDAC) inhibitor MGCD0103 given either daily or 3x
weekly for 14 days every 3 weeks in patients (pts) with advanced solid tumors." Journal of
Clinical Oncology. 2005 ASCO Annual Meeting Proceedings. 23(16S, June 1 Supplement), 2005: 3147 and Kalita et al. "Pharmacodynamic effect of MGCDO103, an oral isotype-selective histone deacetylase (HDAC) inhibitor, on HDAC enzyme inhibition and histone acetylation induction in Phase I clinical trials in patients (pts) with advanced solid tumors or non-Hodgkin's lymphoma (NHL)" Journal of Clinical Oncology. 2005 ASCO Annual Meeting Proceedings. 23(16S, Part I of II, June 1 Supplement), 2005: 9631), a reported thiophenyl derivative of benzamide HDAC inhibitor as presented at the 97th American Association for Cancer Research (AACR) Annual Meeting in Washington, DC. in a poster titled "Enhanced Isotype-Selectivity and Antiproliferative Activity of Thiophenyl Derivatives of Benzamide HDAC Inhibitors In Human Cancer Cells," (abstract #4725), and a reported HDAC inhibitor as described in U.S. Patent 6,541,661; SAHA or Vorinostat (CAS RN 149647-78-9); PXD101 or PXD 101 or PX 105684 (CAS RN 414864-00-9), CI-994 or Tacedinaline (CAS RN 112522-64-2), MS-275 (CAS RN 209783-80-2), or an inhibitor reported in WO2005/108367.

GABA Agents

[0182] In certain embodiments, one or more GABA modulating agents are useful in combination with a first neurogenic agent of the present invention. Non-limiting examples of GABA modulating agents as known to the skilled person and useful herein include the following.

[0183] A GABA modulator is an agent that modulates GABA receptor activity at the receptor level (e.g., by binding directly to GABA receptors), at the transcriptional and/or translational level (e.g., by preventing GABA receptor gene expression), and/or by other modes (e.g., by binding to a ligand or effector of a GABA receptor, or by modulating the activity of an agent that directly or indirectly modulates GABA receptor activity). Non-limiting examples of GABA-A receptor modulators useful in methods described herein include triazolophthalazine derivatives, such as those disclosed in WO 99/25353, and WO/98/04560; tricyclic pyrazolo-pyridazinone analogues, such as those disclosed in WO 99/00391; fenamates, such as those disclosed in 5,637,617; triazolo-pyridazine derivatives, such as those disclosed in WO 99/37649, WO 99/37648, and WO 99/37644; pyrazolo-pyridine derivatives, such as those disclosed in WO 99/43661 and 5,723,462; muscimol, thiomuscimol, and compounds disclosed in 3,242,190; baclofen and compounds disclosed in 3,471,548; phaclofen;
quisqualamine; ZAPA; zaleplon; THIP; imidazole-4-acetic acid (IMA); (+)-bicuculline; gabalinoleamide; isoguvicaine; 3-aminopropane sulphonic acid; piperidine-4-sulphonic acid; 4,5,6,7-tetrahydro-[5,4-c]-pyridin-3-ol; SR 95531; RU5315; CGP 55845; CGP 35348; FG 8094; SCH 5091 i; NG2-73; NGD-96-3; pricROTOXIN and other bicyclophosphates disclosed in Bowery et al., Br. J. Pharmacol., 57; 435 (1976).

[0185] Additional non-limiting examples of GABA-A modulators include compounds described in 6,503,925; 6,218,547; 6,399,604; 6,646,124; 6,515,140; 6,451,809; 6,448,259; 6,448,246; 6,423,711; 6,414,147; 6,399,604; 6,380,209; 6,353,109; 6,297,256; 6,297,252; 6,268,496; 6,21,1365; 6,166,203; 6,177,569; 6,194,427; 6,156,898; 6,143,760; 6,127,395; 6,103,903; 6,103,731; 6,723,735; 6,479,506; 6,476,030; 6,337,331; 6,730,676; 6,730,681; 6,828,322; 6,872,720; 6,699,859; 6,696,444; 6,617,326; 6,608,062; 6,579,875; 6,541,484; 6,500,828; 6,355,798; 6,333,336; 6,319,924; 6,303,605; 6,303,597; 6,291,460; 6,255,305; 6,133,255; 6,872,731; 6,900,215; 6,642,229; 6,593,325; 6,914,060; 6,914,063; 6,914,065; 6,936,608; 6,534,505; 6,426,343; 6,313,125; 6,310,203; 6,200,975; 6,071,909; 5,922,724; 6,096,887; 6,080,873; 6,013,799; 5,936,095; 5,925,770; 5,910,590; 5,908,932; 5,849,927; 5,840,888; 5,817,813; 5,804,686; 5,792,766; 5,750,702; 5,744,603; 5,744,602; 5,723,462; 5,696,260; 5,693,801; 5,677,309; 5,668,283; 5,637,725; 5,637,724; 5,625,063; 5,610,299; 5,608,079; 5,606,059; 5,604,235; 5,585,490; 5,510,480; 5,484,944; 5,473,073; 5,463,054; 5,451,585; 5,426,186; 5,367,077; 5,328,912; 5,326,868; 5,312,822; 5,306,819; 5,286,860; 5,266,698; 5,243,049; 5,216,159; 5,212,310; 5,185,446; 5,185,446; 5,182,290; 5,130,430; 5,095,015; 20050014939; 20040171633; 20050165048; 20050165023; 20040259818; and 20040192692.

[0185] In some embodiments, the GABA-A modulator is a subunit-selective modulator. Non-limiting examples of GABA-A modulator having specificity for the alphal subunit include alpidem and Zolpidem. Non-limiting examples of GABA-A modulator having specificity for the alpha2 and/or alpha3 subunits include compounds described in 6,730,681; 6,828,322; 6,872,720; 6,699,859; 6,696,444; 6,617,326; 6,608,062; 6,579,875; 6,541,484; 6,500,828; 6,355,798; 6,333,336; 6,319,924; 6,303,605; 6,303,597; 6,291,460; 6,255,305; 6,133,255; 6,900,215; 6,642,229; 6,593,325; and 6,914,063. Non-limiting examples of GABA-A modulator having specificity for the alpha2, alpha3 and/or alpha5 subunits include compounds described in 6,730,676 and 6,936,608. Non-limiting examples of GABA-A modulators having specificity for the alpha5 subunit include compounds described in 6,534,505; 6,426,343; 6,313,125; 6,310,203; 6,200,975 and 6,399,604. Additional non-

[0186] In some embodiments, the GABA-A receptor modulator is a reported allosteric modulator. In various embodiments, allosteric modulators modulate one or more aspects of the activity of GABA at the target GABA receptor, such as potency, maximal effect, affinity, and/or responsiveness to other GABA modulators. In some embodiments, allosteric modulators potentiate the effect of GABA (e.g., positive allosteric modulators), and/or reduce the effect of GABA (e.g., inverse agonists). Non-limiting examples of benzodiazepine GABA-A modulators include alprazolam, benzazepam, brexazenil, bromazepam, brotizolam, cannazepam, chlordiazepoxide, clobazam, clonazepam, cinolazepam, clonazepam, cloxazolam, clozapin, delorazepam, diazepam, dibenzepin, dipotassium chlorazepate, divaplon, estazolam, ethyl-loflazepate, etizolam, fludiazepam, flumazenil, flunitrazepam, flurazepam HCl, fluprazepam, halazepam, haloxazolam, imidazienil, ketazolam, lorazepam, loprazolam, lormetazepam, medazepam, metaclozepam, mexozolam, midazolam-HCl, nabanizil, nimetazepam, nitrazepam, nordazepam, oxazepam-tazepam, oxazolam, pinazepam, prazepam, quazepam, sarmazenil, suriclone, temazepam, tetrazepam, tofisopam, triazolam, zaleplon, zalezepam, Zolpidem, zopiclone, and zopielon.


[0188] Non-limiting examples of barbiturate or barbituric acid derivative GABA-A modulators include phenobarbital, pentobarbital, pentobarbentine, primidone, barbexaclon, dipropyl barbituric acid, eunarcon, hexobarbital, mephobarbital, methohexital, Nα-methohexitol, 2,4,6(1H,3H,5)-pyrimidintrione, secbutabarbital and/or thiopental.

[0189] Non-limiting examples of neurosteroid GABA-A modulators include alphaxalone, allotetrahydrodeoxycorticosterone, tetrahydrodeoxycorticosterone, estrogen, progesterone 3beta-hydroxyandrost-5-en-1 7-on-3-sulfate, dehydroepianrosterone, eltanolone,
ethinylestradiol, 5-pregnen-3-beta-ol-20 on-sulfate, 5α-pregnan-3β-ol-20-one (5PG),
allopregnanolone, pregnanolone, and steroid derivatives and metabolites described in
5,939,545, 5,925,630, 6,277,838, 6,143,736, RE35,517, 5,925,630, 5,591,733, 5,232,917,
20050179676, WO 961 16076, WO 98/05337, WO 95/21617, WO 94/27608, WO 93/18053,

Non-limiting examples of beta-carboline GABA-A modulators include abecarnil,
3,4-dihydro-beta-carboline, gedocarnil, 1-methyl-1-vinyl-2,3,4-trihydro-beta-carboline-3-
carboxylic acid, 6-methoxy-1,2,3,4-tetrahydro-beta-carboline, N-BOC-L- 1,2,3,4-tetrahydro-
beta-carboline-3-carboxylic acid, tryptoline, pinoline, methoxyharmalan, tetrahydro-beta-
carboline (THBC), 1-methyl-THBC, 6-methoxy-THBC, 6-hydroxy-THBC, 6-
methoxyharmalan, norharman, 3,4-dihydro-beta-carboline, and compounds described in

Non-limiting examples of reported GABA-B receptor modulators useful in methods
described herein include CGP36742; CGP-64213; CGP 56999A; CGP 54433A; CGP 36742;
SCH 50911; CGP 7930; CGP 13501; baclofen and compounds disclosed in 3,471,548;
sacrofen; phaclofen; 2-hydroxysacrofen; SKF 97541; CGP 35348 and related compounds
described in Hills, et al, Br. J. Pharmacol., 102, pp. 5-6 (1991); and compounds described in

Non-limiting examples of reported GABA-C receptor modulators useful in methods
described herein include cis-aminocrotonic acid (CACA); 1,2,5,6-tetrahydropyridine-4-yl
methyl phosphinic acid (TPMPA) and related compounds such as P4MPA, PPA and SEPI; 2-
methyl-TACA; (+A)-TAMP; muscimol and compounds disclosed in 3,242,190; ZAPA; THIP

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and related analogues, such as aza-THIP; pricotroxin; imidazole-4-acetic acid (IMA); and CGP36742.

[0193] In some embodiments, the GABA modulator modulates the activity of glutamic acid decarboxylase (GAD).

[0194] In some embodiments, the GABA modulator modulates GABA transaminase (GTA). Non-limiting examples of GTA modulators include the GABA analogue vigabatrin and compounds disclosed in 3,960,927.

[0195] In some embodiments, the GABA modulator modulates the reuptake and/or transport of GABA from extracellular regions. In other embodiments, the GABA modulator modulates the activity of the GABA transporters, GAT-1, GAT-2, GAT-3 and/or BGT-1. Non-limiting examples of GABA reuptake and/or transport modulators include nipecotic acid and related derivatives, such as CI 966; SKF 89976A; TACA; stiripentol; tiagabine and GAT-1 inhibitors disclosed in 5,010,090; (R)-l-(4,4-diphenyl-3-butenyl)-3-piperidinecarboxylic acid and related compounds disclosed in 4,383,999; (R)-l-[4,4-bis(3-methyl-2-thienyl)-3-butenyl]-3-piperidinecarboxylic acid and related compounds disclosed in Anderson et al., J. Med. Chem. 36, (1993) 1716-1725; guvacine and related compounds disclosed in Krosggaard-Larsen, Molecular & Cellular Biochemistry 31, 105-121 (1980); GAT-4 inhibitors disclosed in 6,071,932; and compounds disclosed in 6,906,177 and Ali, F. E., et al. J. Med. Chem. 1985, 28, 653-660. Methods for detecting GABA reuptake inhibitors are known in the art, and are described, e.g., in 6,906,177; 6,225,115; 4,383,999; Ali, F. E., et al. J. Med. Chem. 1985, 28, 653-660.

[0196] In some embodiments, the GABA modulator is the benzodiazepine Clonazepam, which is described, e.g., in 3,121,076 and 3,116,203; the benzodiazepine Diazepam, which is described, e.g., in 3,371,085; 3,109,843; and 3,136,815; the short-acting diazepam derivative Midazolam, which is a described, e.g., in 4,280,957; the imidazodiazepine Flumazenil, which is described, e.g., in 4,316,839; the benzodiazepine Lorazepam is described, e.g., in 3,296,249; the benzodiazepine L-655708, which is described, e.g., in Quirk et al. Neuropharmacology 1996, 35, 1331; Sur et al. Mol. Pharmacol. 1998, 54, 928; and Sur et al. Brain Res. 1999, 822, 265; the benzodiazepine Gabitril; Zopiclone, which binds the benzodiazepine site on GABA-A receptors, and is disclosed, e.g., in 3,862,149 and 4,220,646; the GABA-A potentiator Indiplon as described, e.g., in Foster et al., J Pharmacol Exp Ther., 311(2):547-59 (2004), 4,521,422 and 4,900,836; Zolpidem, described, e.g., in
Neurosci Lett. 1988;92(1):92-6; the GABA-B antagonist 2-Hydroxysaclofen, which is described, e.g., in Kerr et al. Neurosci. Lett. 1988, 92, 92; and Curtis et al. Neurosci. Lett. 1988, 92, 97; the GABA-B antagonist SCH 50,911, which is described, e.g., in Carruthers et al., Bioorg Med Chem Lett 8: 3059-3064 (1998); Bolser et al. J. Pharmacol. Exp. Ther. 1996, 274, 1393; Hosford et al. J. Pharmacol. Exp. Ther. 1996, 274, 1399; and Ong et al. Eur. J. Pharmacol. 1998, 362, 35; the selective GABA-C antagonist TPMPA, which is described, e.g., in Schlicker et al., Brain Res. Bull. 2004, 63(2), 91-7; Murata et al., Bioorg. Med. Chem. Lett. 6: 2073 (1996); and Ragozzino et al., Mol. Pharmacol., 50: 1024 (1996); a GABA derivative, such as Pregabalin [(S)-(−)-3-isobutylgaba] or gabapentin [1-(aminomethyl)cyclohexane acetic acid]. Gabapentin is described, e.g., in U.S. Patent 4,024,175; the lipid-soluble GABA agonist Progabide, which is metabolized in vivo into GABA and/or pharmaceutically active GABA derivatives in vivo. Progabide is described, e.g., in U.S. Patents 4,094,992 and 4,361,583; the GAT1 inhibitor Tiagabine, which is described, e.g., in U.S. Patent 5,010,090 and Andersen et al. J. Med. Chem. 1993, 36, 1716; the GABA transaminase inhibitor Valproic Acid (2-propylpentanoic acid or dispropylacetic acid), which is described, e.g., in U.S. Patent 4,699,927 and Carraz et al., Therapie., 1965, 20, 419; the GABA transaminase inhibitor Vigabatrin, which is described, e.g., in U.S. Patent 3,960,927; or Topiramate, which is described, e.g., in U.S. Patent 4,513,006.

**Epileptic Agents**

[0197] In certain embodiments, one or more anti-epileptic agents are useful in combination with a first neurogenic agent of the present invention. Non-limiting examples of anti-epileptic agents as known to the skilled person and useful herein include carbamazepine or tegretol (CAS RN 298-46-4), clonazepam (CAS RN 1622-61-3), BPA or 3-(p-Borophenyl)alanine (CAS RN 90580-64-6), gabapentin or neurontin (CAS RN 60142-96-3), phenytoin (CAS RN 57-41-0), topiramate, lamotrigine or lamictal (CAS RN 84057-84-1), phenobarbital (CAS RN 50-06-6), oxcarbazepine (CAS RN 28721-07-5), primidone (CAS RN 125-33-7), ethosuximide (CAS RN 77-67-8), levetiracetam (CAS RN 102767-28-2), zonisamide, tiagabine (CAS RN 115103-54-3), depakote or divalproex sodium (CAS RN 76584-70-8),Felbamate (Na-channel and NMDA receptor antagonist), or pregabalin (CAS RN 148553-50-8).
Dopamine Agents

In certain embodiments, one or more direct or indirect agents that modulate dopamine receptors are useful in combination with a first neurogenic agent of the present invention. Non-limiting examples of such agents as known to the skilled person and useful herein include the indirect dopamine agonists methylphenidate (CAS RN 113-45-1) or Methylphenidate hydrochloride (also known as ritalin CAS RN 298-59-9), amphetamine (CAS RN 300-62-9) and methamphetamine (CAS RN 537-46-2), and the direct dopamine agonists sumanirole (CAS RN 179386-43-7), roprinirole (CAS RN 91374-21-9), and rotigotine (CAS RN 99755-59-6). Additional non-limiting examples include 7-OH-DPAT, quinpirole, haloperidole, or clozapine.

Additional non-limiting examples include bromocriptine (CAS RN 25614-03-3), adroglide (CAS RN 171752-56-0), pramipexole (CAS RN 104632-26-0), Ropinirole (CAS RN 91374-21-9), apomorphine (CAS RN 58-00-4) or apomorphine hydrochloride (CAS RN 314-19-2), lisuride (CAS RN 18016-80-3), Sibenadet hydrochloride or Viozan (CAS RN 154189-24-9), L-DOPA or Levodopa (CAS RN 59-92-7), Melevodopa (CAS RN 7101-51-1), etilevodopa (CAS RN 37178-37-3), Talipexole hydrochloride (CAS RN 36085-73-1) or Talipexole (CAS RN 101626-70-4), Nolomirole (CAS RN 90060-42-7), quinelorane (CAS RN 97466-90-5), pergolide (CAS RN 66104-22-1), fenoldopam (CAS RN 67227-56-9), Carmoxirole (CAS RN 98323-83-2), terguride (CAS RN 37686-84-3), cabergoline (CAS RN 81409-90-7), quinagolide (CAS RN 87056-78-8) or quinagolide hydrochloride (CAS RN 94424-50-7), sumanirole, docarpamine (CAS RN 74639-40-0), SLV-308 or 2(3H)-Benzoxazolone, 7-(4-methyl-l-piperazinyl)-monohydrochloride (CAS RN 269718-83-4), aripiprazole (CAS RN 129722-12-9), bifeprunox, lisdexamfetamine dimesylate (CAS RN 608137-33-3), safinamide (CAS RN 133865-89-1), or Adderall or Amfetamine (CAS RN 300-62-9).

Dual Sodium and Calcium Channel Agents

In certain embodiments, one or more dual sodium and calcium channel modulatory agents are useful in combination with a first neurogenic agent of the present invention. Non-limiting examples of such agents as known to the skilled person and useful herein include the following.
Non-limiting examples of dual sodium and calcium channel modulating agents include safinamide and zonisamide. Additional non-limiting examples include enecadin (CAS RN 259525-01-4), Levosemotiadil (CAS RN 116476-16-5), bisaramil (CAS RN 89194-77-4), SL-34.0829 (see U.S. Patent 6,897,305), lifarizine (CAS RN 119514-66-8), JTV-519 (4-[3-(4-benzylpiperidin-1-yl)propionyl]-7-methoxy-2,3,4,5-tetrahydron-1,4-benzothiazepine monohydrochloride), and delapril.

**Calcium Channel Agents**

In certain embodiments, one or more calcium channel antagonistic agents are useful in combination with a first neurogenic agent of the present invention. Non-limiting examples of such agents as known to the skilled person and useful herein include the following.

Certain embodiments include, without limitation, calcium channel antagonist such as amlodipine (CAS RN 88150-42-9) or amlodipine maleate (CAS RN 88150-47-4), nifedipine (CAS RN 21829-25-4), MEM-1003 (CAS RN see Rose et al. "Efficacy of MEM 1003, a novel calcium channel blocker, in delay and trace eyeblink conditioning in older rabbits." Neurobiol Aging. 2006 Apr 16; [electronically published ahead of print]), isradipine (CAS RN 75695-93-1), felodipine (CAS RN 72509-76-3; 3,5-Pyridinedicarboxylic acid, 1,4-dihydro-4-(2,3-dichlorophenyl)-2,6-dimethyl-, ethyl methyl ester) or felodipine (CAS RN 86189-69-7; 3,5-Pyridinedicarboxylic acid, 4-(2,3-dichlorophenyl)-1,4-dihydro-2,6-dimethyl-, ethyl methyl ester, (+-)), lemildipine (CAS RN 125729-29-5 or 94739-29-4), clevidipine (CAS RN 166432-28-6 or 167221-71-8), verapamil (CAS RN 52-53-9), ziconotide (CAS RN 107452-89-1), monatepil maleate (CAS RN 132046-06-1), manidipine (CAS RN 89226-50-6), Furnidipine (CAS RN 138661-03-7), Nitrendipine (CAS RN 39562-70-4), Loperamide (CAS RN 53179-11-6), Amiodarone (CAS RN 1951-25-3), Bepridil (CAS RN 64706-54-3), diltiazem (CAS RN 42399-41-7), Nimodipine (CAS RN 66085-59-4), Lamotrigine, Cinnarizine (CAS RN 298-57-7), lacipidine (CAS RN 103890-78-4), nilvadipine (CAS RN 75530-68-6), dotarizine (CAS RN 84625-59-2), cilnidipine (CAS RN 132203-70-4), Oxodipine (CAS RN 90729-41-2), aranidipine (CAS RN 86780-90-7), anipamil (CAS RN 83200-10-6), ipenoxazine (CAS RN 104454-71-9), Efondipine hydrochloride or NZ 105 (CAS RN 11101 1-53-1) or Efondipine (CAS RN 11101 1-63-3), temiverine (CAS RN 173324-94-2), pranidipine (CAS RN 99522-79-9), dopropidil (CAS RN 79700-61-1), lercanidipine (CAS RN 100427-26-7), terodiline (CAS RN 15793-40-5), fantofarone (CAS RN 114432-13-2), azelnidipine (CAS RN 123524-52-7), mibefradil (CAS RN 116644-53-2)

Melatonin Receptor Agents

[0204] In certain embodiments, one or more melatonin receptor modulatory agents are useful in combination with a first neurogenic agent of the present invention. Non-limiting examples of such agents as known to the skilled person and useful herein include the following.

[0205] Non-limiting examples of modulators of the melatonin receptor include the melatonin receptor agonists melatonin, LY-156735 (CAS RN 118702-11-7), agomelatine (CAS RN 1381 12-76-2), 6-chloromelatonin (CAS RN 63762-74-3), Ramelteon (CAS RN 196597-26-9), 2-Methyl-6,7-dichloromelatonin (CAS RN 104513-29-3), and ML 23 (CAS RN 108929-03-9).

Melanocortin Receptor Agents

[0206] In certain embodiments, one or more melanocortin receptor agents are useful in combination with a first neurogenic agent of the present invention. Non-limiting examples of melanocortin receptor agents as known to the skilled person and useful herein include the following.
Non-limiting examples of such agents include a melanocortin receptor agonists selected from melanotan II (CAS RN 121062-08-6), PT-141 or Bremelanotide (CAS RN 189691-06-3), HP-228 (see Getting et al. "The melanocortin peptide HP228 displays protective effects in acute models of inflammation and organ damage." Eur J Pharmacol. 2006 Jan 24), or AP214 from Action Pharma A/S.

Angiotensin II Agents

In certain embodiments, one or more angiotensin II modulatory agents are useful in combination with a first neurogenic agent of the present invention. Non-limiting examples of such agents as known to the skilled person and useful herein include the following.

Non-limiting examples include a modulator of angiotensin II function, such as at an angiotensin II receptor. In some embodiments, agent may be an inhibitor of an angiotensin converting enzyme (ACE). Non-limiting examples of ACE inhibitors include a sulfhydryl-containing (or mercapto-containing) agent, such as Alacepril, captopril (Capoten®), fentiapril, pivopril, pivalopril, or zofenopril; a dicarboxylate-containing agent, such as enalapril (Vasotec® or Renitec®) or enalaprilat, ramipril (Altace® or Tritace® or Ramace®), quinapril (Accupril®) or quinapril hydrochloride, perindopril (Coversyl®) or perindopril erbumine (Aceon®), lisinopril (Lisodur® or Prinivil® or Zestril®); a phosphate-containing (or phosphate-containing) agent, such as fosinopril (Monopril®), fosinoprilat, fosinopril sodium (CAS RN 88889-14-9), benazepril (Lotensin®) or benazepril hydrochloride, imidapril or imidapril hydrochloride, moexipril (Univasc®), or trandolapril (Mavik®). In other embodiments, a modulator is administered in the form of an ester that increases bioavailability upon oral administration with subsequent conversion into metabolites with greater activity.

Further embodiments include reported angiotensin II modulating entities that are naturally occurring, such as casokinins and lactokinins (breakdown products of casein and whey) which may be administered as such to obviate the need for their formation during digestion. Additional non-limiting embodiments of reported angiotensin receptor antagonists include candesartan (Atacand® or Ratacand®, 139481-59-7) or candesartan cilexetil; eprosartan (Teveten®) or eprosartan mesylate; irbesartan (Aprovel® or Karvea® or Avapro®); losartan (Cozaar® or Hyzaar®); olmesartan (Benicar®, CAS RN 144689-24-7) or
olmesartan medoxomil (CAS RN 144689-63-4); telmisartan (Micardis® or Pritor®); or valsartan (Diovan®).

Additional non-limiting examples of a reported angiotensin modulator that may be used in a combination include nateglinide or starlix (CAS RN 105816-04-4); tasosartan or its metabolite enoltasosartan; omapatrilat (CAS RN 167305-00-2); or a combination of nateglinide and valsartan, amoldipine and benazepril (Lotrel 10-40 or Lotrel 5-40), or delapril and manidipine (CHF 1521). In some embodiments, the second agent may be an inhibitor of renin, for example, aliskiren (CAS RN 17334-57-1) which is sold under the name TEKTURNA.

5HT (Serotonin) Agents

In certain embodiments, one or more 5-hydroxytryptamine (5HT, or serotonin) agents are useful in combination with a first neurogenic agent of the present invention. Non-limiting examples of 5HT agents as known to the skilled person and useful herein include the following.

Non-limiting examples include a 5HT1a receptor agonist (or partial agonist) such as buspirone (buspar). In some embodiments, a reported 5HT1a receptor agonist is an azapirone, such as, but not limited to, tandospirone, gepirone and ipsapirone. Non-limiting examples of additional reported 5HT1a receptor agonists include flesinoxan (CAS RN 98206-10-1), MDL 72832 hydrochloride, U-92016A, (+)-UH 301, F 13714, F 13640, 6-hydroxy-buspirone (see US 2005/0137206), S-6-hydroxy-buspirone (see US 2003/0022899), R-6-hydroxy-buspirone (see US 2003/0009851), adatanserin, buspirone-saccharide (see WO 00/12067) or 8-hydroxy-2-dipropylaminotetralin (8-OHDPAT).

Additional non-limiting examples of reported 5HT1a receptor agonists include OPC-14523 (l-[3-[4-(3-chlorophenyl)-l-piperazinyl]propyl]-5-methoxy-3,4-dihydro-2[lH]-quinolinone monomethanesulfonate); BMS-181 100 or BMY 14802 (CAS RN 105565-56-8); flibanserin (CAS RN 167933-07-5); repinotan (CAS RN 144980-29-0); lesopitron (CAS RN 132449-46-8); piclozotan (CAS RN 182415-09-4); Aripiprazole, Qrg-1301 1 (l-(4-trifluoromethyl-2-pyridinyl)-4- [4-[2-oxo-1-pyrrolidinyl]butyl]piperazine (E)-2-butenedioate); SDZ-MAR-327 (see Christian et al. "Positron emission tomographic analysis of central dopamine D1 receptor binding in normal subjects treated with the atypical neuroleptic, SDZ MAR 327." Int J Mol Med. 1998 l(l):243-7); MKC-242 ((S)-5-[3-[(1,4-
benzodioxan-2-ylmethyl)amino]propoxy]-1,3-benzodioxole HCl); vilazodone; sarizotan
(CAS RN 177975-08-5); roxindole (CAS RN 112192-04-8) or roxindole methanesulfonate
(CAS RN 119742-13-1); alnespirone (CAS RN 138298-79-0); bromerguride (CAS RN
83455-48-5); xaliproden (CAS RN 135354-02-8); mazapertine succinate (CAS RN 134208-
18-7) or mazapertine (CAS RN 134208-17-6); PRX-00023; F-13640 ((3-chloro-4-fluoro-
phenyl)-4-fluoro-4-[[[5-methyl-pyridin-2-ylmethyl]-amino]methyl]piperidin-1-
ylmethanone, fumaric acid salt); eptapirone (CAS RN 179756-85-5); Ziprasidone (CAS RN
146939-27-7); Sunepitron (see Becker et al. "G protein-coupled receptors: In silico drug
discovery in 3D" PNAS 2004 101(31):1304-1309); umespirone (CAS RN 107736-98-1);
SLV-308; bifeprunox; and zalospirone (CAS RN 114298-18-9). Yet further non-limiting
examples include AP-521 (partial agonist from AsahiKasei) and Du-123015 (from Solvay).

[0215] In certain embodiments, the agent may be a reported 5HT4 receptor agonist (or
partial agonist). In some embodiments, a reported 5HT4 receptor agonist or partial agonist is
a substituted benzamide, such as cisapride; individual, or a combination of, cisapride
enantiomers ((+) cisapride and (-) cisapride); mosapride; and renzapride as non-limiting
examples. In other embodiments, the chemical entity is a benzofuran derivative, such as
prucalopride. Additional embodiments include indoles, such as tegaserod, or
benzimidazolones. Other non-limiting chemical entities reported as a 5HT4 receptor agonist
or partial agonist include zacopride (CAS RN 90182-92-6), SC-531 16 (CAS RN 141196-99-
8) and its racemate SC-49518 (CAS RN 146388-57-0), BIMU1 (CAS RN 127595-43-1), TS-
951 (CAS RN 174486-39-6), or ML10302 CAS RN 148868-55-7). Additional non-limiting
chemical entities include metoclopramide, 5-methoxytryptamine, RS67506, 2-[1-(4-
piperonyl)piperazinyl]benzothiazole, RS66331, BIMU8, SB 205149 (the n-butyl quaternary
analog of renzapride), or an indole carbazimidamide as described by Buchheit et al. ("The
serotonin 5-HT4 receptor. 2. Structure-activity studies of the indole carbazimidamide class of
norcisapride (CAS RN 102671-04-5) which is the metabolite of cisapride; mosapride citrate;
the maleate form of tegaserod (CAS RN 189188-57-6); zacopride hydrochloride (CAS RN
99617-34-2); mezacopride (CAS RN 89613-77-4); SK-951 ((+)-4-amino-N-(2-(l-
azabicyclo(3.3.0)octan-5-yl)ethyl)-5-chloro-2,3-dihydro-2-methylbenzo(b)furan-7-
carboxamide hemifumarate); ATI-7505, a cisapride analog from ARYx Therapeutics; SDZ-
216-454, a selective 5HT4 receptor agonist that stimulates cAMP formation in a
concentration dependent manner (see Markstein et al. "Pharmacological characterisation of 5-
HT receptors positively coupled to adenylyl cyclase in the rat hippocampus." Naunyn Schmiedebergs Arch Pharmacol. (1999) 359(6):454-9; SC-54750, or Aminomethylazaadamantane; Y-36912, or 4-amino-N-[l-3-(benzylsulfonyl)propyl]piperidin-4-ylmethyl]-5-chloro-2-methoxybenzamide as disclosed by Sonda et al. ("Synthesis and pharmacological properties of benzamide derivatives as selective serotonin 4 receptor agonists." Bioorg Med Chem. (2004) 12(10):2737-47); TKS 159, or 4-amino-5-chloro-2-methoxy-N-[(2S,4S)-1-ethyl-2- hydroxymethyl-4-pyrrolidinyl] benzamide, as reported by Haga et al. ("Effect of TKS 159, a novel 5-hydroxytryptamine4 agonist, on gastric contractile activity in conscious dogs."); RS67333, or l-(4-amino-5-chloro-2-methoxyphenyl)-3-(l -n-butyl-4-piperidinyl)- 1-propanone; KDR-5 169, or 4-amino-5-chloro-N-[l-(3-fluoro-4-methoxybenzyl)piperidin-4-yl]-2-(2-hydroxyethoxy)benzamide hydrochloride dihydrate as reported by Tazawa, et al. (2002) "KDR-5 169, a new gastrointestinal prokinetic agent, enhances gastric contractile and emptying activities in dogs and rats." Eur J Pharmacol 434(3): 169-76; SL65.0155, or 5-(8-amino-7-chloro-2,3-dihydro-1,4-benzodioxin-5-yl)-3-[l -(2-phenyl ethyl)-4-piperidinyl]- 1,3,4-oxadiazol-2(3H)-one monohydrochloride; and Y-34959, or 4-Amino-5-chloro-2-methoxy-N-[l-[5-(l-methylindol-3-yl)carbonyl]amino]pentyl]piperidin-4-ylmethyl]benzamide.

[0216] Other non-limiting reported 5HT4 receptor agonists and partial agonists include metoclopramide (CAS RN 364-62-5), 5-methoxytryptamine (CAS RN 608-07-1), RS67506 (CAS RN 168986-61-6), 2-[(4-piperonyl)piperazinyl]benzothiazole (CAS RN 155106-73-3), RS66331 (see Buccafusco et al. "Multiple Central Nervous System Targets for Eliciting Beneficial Effects on Memory and Cognition." (2000) Pharmacology 295(2):438-446), BIMU8 (endo-N-8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-2,3-dehydro-2-oxo-3-(prop-2-yl)-1H-benzoimidazole-1-carboxamide), or SB 25149 (the n-butyl quaternary analog of renzapride). Compounds related to metoclopramide, such as metoclopramide dihydrochloride (CAS RN 2576-84-3) or metoclopramide dihydrochloride (CAS RN 5581-45-3) or metoclopramide hydrochloride (CAS RN 7232-21-5 or 54143-57-6) may also be used in a combination or method as described herein.

[0217] In certain embodiments, the agent may be a reported 5HT3 receptor antagonist such as azasetron (CAS RN 123039-99-6); Ondansetron (CAS RN 99614-02-5) or Ondansetron hydrochloride (CAS RN 99614-01-4); Cilansetron (CAS RN 120635-74-7); Aloxi or Palonosetron Hydrochloride (CAS RN 135729-62-3); Palonosetron (CAS RN 135729-61-2 or 135729-56-5); Cisplatin (CAS RN 15663-27-1); Lotronex or Alosetron hydrochloride (CAS
RN 122852-69-1; Anzemet or Dolasetron mesylate (CAS RN 115956-13-3); zacopride or R-
Zacopride; E-3620 [(3S)-endo]-4-amino-5-chloro-N-(8-methyl-8-azabicyclo[3.2.1]oct-3-
yl-2[(1-methyl-2-butynyl)oxy]benzamide) or E-3620 HCl (3(S)-endo-4-amino-5-chloro-N-
(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-2-(1-methyl-2-butynyl)oxy)-benzamide-HCl); YM
060 or Ramosetron hydrochloride (CAS RN 132907-72-3); a thieno[2,3-d]pyrimidine
derivative antagonist described in U.S. Patent 6,846,823, such as DDP 225 or MCI 225 (CAS
RN 135991-48-9); Marinol or Dronabinol (CAS RN 1972-08-3); or Lac Hydrin or
Ammonium lactate (CAS RN 515-98-0); Kytril or Granisetron hydrochloride (CAS RN
107007-99-8); Bemesetron (CAS RN 40796-97-2); Tropisetron (CAS RN 89565-68-4);
Zatosteron (CAS RN 123482-22-4); Mirisetron (CAS RN 135905-89-4) or Mirisetron
maleate (CAS RN 14861-75-0); or renzapride (CAS RN 112727-80-7).

[0218] In certain embodiments, the agent may be a reported 5HT2A/2C receptor antagonist
such as Ketanserin (CAS RN 74050-98-9) or ketanserin tartrate; risperidone; olanzapine;
adatanserin (CAS RN 127266-56-2); Ritanserin (CAS RN 87051-43-2); etoperidone;
nefazodone; deramciclane (CAS RN 120444-71-5); Geodon or Ziprasidone hydrochloride
(CAS RN 138982-67-9); Zeldox or Ziprasidone or Ziprasidone hydrochloride; EMD 281014
(7-[4-[2-(4-fluoro-phenyl)-ethyl] -piperazine-1-carbonyl]-1H-indole-3-carbonitrile HCl);
MDL 100907 or M100907 (CAS RN 139290-65-6); Effexor XR (Venlafaxine formulation);
Zomaril or Iloperidone; quetiapine (CAS RN 111974-69-7) or Quetiapine fumarate (CAS RN
111974-72-2) or Seroquel; SB 228357 or SB 243213 (see Bromidge et al.
"Biarylcarbamoylindolines are novel and selective 5-HT(2C) receptor inverse agonists:
identification of 5-methyl-l-[2-[2-(methyl-3-pyridyl)oxy]5-pyridyl]carbamoyl]-6-
trifluoromethylindoline (SB-243213) as a potential antidepressant/anxiolytic agent." J Med
Chem. 2000 43(6): 1123-34; SB 220453 or Tonabersat (CAS RN 175013-84-0); Sertindole
(CAS RN 1065 16-24-9); Eplivanserin (CAS RN 130579-75-8) or Eplivanserin fumarate
(CAS RN 130580-02-8); Lubazodone hydrochloride (CAS RN 161 178-10-5);
Cyproheptadine (CAS RN 129-03-3); Pizotyline or pizotifen (CAS RN 15574-96-6);
Mesulergine (CAS RN 64795-35-3); Irindalone (CAS RN 96478-43-2); MDL 11939 (CAS
RN 107703-78-6); or pruvanserin (CAS RN 443144-26-1).

[0219] Additional non-limiting examples of modulators include reported 5-HT2 agonists
or partial agonists, such as m-chlorophenylpiperazine; or 5-HT2A receptor inverse agonists,
such as ACP 103 (CAS RN: 868855-07-6), APD125 (from Arena Pharmaceuticals), AVE
8488 (from Sanofi-Aventis) or TGWOOAD/AA(from Fabre Kramer Pharmaceuticals).
In certain embodiments, the agent may be a reported 5HT6 receptor antagonist such as SB-357 134 (N-(2,5-Dibromo-3-fluorophenyl)-4-methoxy-3-piperazin-1-ylbenzenesulfonamide); SB-27 1046 (5-chloro-N-(4-methoxy-3-(piperazin-1-yl)phenyl)-3-methylbenzo[b]thiophene-2-sulfonamide); Ro 04-06790 (N-(2,6-bis(methylamino)pyrimidin-4-yl)-4-aminobenzenesulfonamide); Ro 63-0563 (4-amino-N-(2,6-bis(methylamino-pyridin-4-yl)-benzene sulfonamide); clozapine or its metabolite N-desmethylclozapine; olanzapine (CAS RN 132539-06-1); fluperlapine (CAS RN 67121-76-0); Seroquel (quetiapine or quetiapine fumarate); clomipramine (CAS RN 303-49-1); amitriptyline (CAS RN 50-48-6); doxepin (CAS RN 1668-19-5); nortriptyline (CAS RN 72-69-5); 5-methoxytryptamine (CAS RN 608-07-1); bromocryptine (CAS RN 50-53-3); loxapine (CAS RN 1977-10-2); fluphenazine (CAS RN 69-23-8); or GSK 742457 (presented by David Witty, "Early Optimisation of in vivo Activity: the discovery of 5-HT6 Receptor Antagonist 742457" GlaxoSmithKline at SCIpharm 2006, International Pharmaceutical Industry Conference in Edinburgh, 16 May 2006).

As an additional non-limiting example, the reported 5HT6 modulator may be SB-258585 (4-Iodo-N-[4-methoxy-3-(4-methyl-piperazin-1-yl)-phenyl]-benzenesulphonamide); PRX 07034 (from Predix Pharmaceuticals) or a partial agonist, such as E-6801 (6-chloro-N-(3-(2-(dimethylamino)ethyl)-1H-indol-5-yl)imidazo[2,1-b]thiazole-5-sulfonamide) or E-6837 (5-chloro-N-(3-(2-(dimethylamino)ethyl)-1H-indol-5-yl)naphthalene-2-sulfonamide).

Monoamines and Other Biogenic Amine Agents

In certain embodiments, one or more monoamines or other biogenic amine agents are useful in combination with a first neurogenic agent of the present invention. Non-limiting examples of such agents as known to the skilled person and useful herein include the following.

In certain embodiments, a monoamine modulator that modulates neurotransmission mediated by one or more monoamine neurotransmitters (referred to herein as "monoamines") or other biogenic amines, such as trace amines (TAs) is a useful agent, as a non-limiting example. TAs are endogenous, CNS-active amines that are structurally related to classical biogenic amines (e.g., norepinephrine, dopamine (4-(2-aminoethyl)benzene-1,2-diol), and/or serotonin (5-hydroxytryptamine (5-HT), or a metabolite, precursor, prodrug, or analogue.
thereof. The methods of the disclosure thus include administration of one or more reported TAs in a combination with a first neurogenic agent. Additional CNS-active monoamine receptor modulators are well known in the art, and are described, e.g., in the Merck Index, 12th Ed. (1996).

[0224] Certain food products, e.g., chocolates, cheeses, and wines, can also provide a significant dietary source of TAs and/or TA-related compounds. Non-limiting examples of mammalian TAs useful as constitutive factors include, but are not limited to, tryptamine, p-tyramine, m-tyramine, octopamine, synephrine or β-phenylethylamine (β-PEA). Additional useful TA-related compounds include, but are not limited to, 5-hydroxytryptamine, amphetamine, bufotenin, 5-methoxytryptamine, dihydromethoxytryptamine, phenylephrine, or a metabolite, precursor, prodrug, or analogue thereof.

[0225] In some embodiments, the constitutive factor is a biogenic amine or a ligand of a trace amine-associated receptor (TAAR), and/or an agent that mediates one or more biological effects of a TA. TAs have been shown to bind to and activate a number of unique receptors, termed TAARs, which comprise a family of G-protein coupled receptors (TAARl-TAAR9) with homology to classical biogenic amine receptors. For example, TAAR1 is activated by both tyramine and β-PEA.

[0226] Thus non-limiting embodiments include methods and combination compositions wherein the constitutive factor is β-PEA, which has been indicated as having a significant neuromodulatory role in the mammalian CNS and is found at relatively high levels in the hippocampus (e.g., Taga et al., Biomed Chromatogr., 3(3): 118-20 (1989)); a metabolite, prodrug, precursor, or other analogue of β-PEA, such as the β-PEA precursor L-phenylalanine, the β-PEA metabolite β-phenylacetic acid (β-PAA), or the β-PEA analogues methylphenidate, amphetamine, and related compounds.

[0227] Most TAs and monoamines have a short half-life (e.g., less than about 30 s) due, e.g., to their rapid extracellular metabolism. Thus embodiments of the disclosure include use of a monoamine "metabolic modulator," which increases the extracellular concentration of one or more monoamines by inhibiting monoamine metabolism. In some embodiments, the metabolic modulator is an inhibitor of the enzyme monoamine oxidase (MAO), which catalyzes the extracellular breakdown of monoamines into inactive species. Isoforms MAO-A and/or MAO-B provide the major pathway for TA metabolism. Thus, in some embodiments, TA levels are regulated by modulating the activity of MAO-A and/or MAO-B. For example,
in some embodiments, endogenous TA levels are increased (and TA signaling is enhanced) by administering an inhibitor of MAO-A and/or MAO-B.

[0228] Non-limiting examples of inhibitors of monoamine oxidase (MAO) include reported inhibitors of the MAO-A isoform, which preferentially deaminates 5-hydroxytryptamine (serotonin) (5-HT) and norepinephrine (NE), and/or the MAO-B isoform, which preferentially deaminates phenylethylamine (PEA) and benzylamine (both MAO-A and MAO-B metabolize Dopamine (DA)). In various embodiments, MAO inhibitors may be irreversible or reversible (e.g., reversible inhibitors of MAO-A (RIMA)), and may have varying potencies against MAO-A and/or MAO-B (e.g., non-selective dual inhibitors or isoform-selective inhibitors). Non-limiting examples of MAO inhibitors useful in methods described herein include clorgyline, L-deprenyl, isocarboxazid (Marplan), ayahuasca, nialamide, iproniazide, iproclozide, moclobemide (Aurorix), phenelzine (Nardil), tranylcypromine (Parnate) (the congeneric of phenelzine), toloxatone, levo-deprenyl (Selegilene), harmala, RIMAs (e.g., moclobemide, described in Da Prada et al., J Pharmacol Exp Ther 248: 400-414 (1989); brofaromine; and befloxatone, described in Curet et al., J Affect Disord 51: 287-303 (1998)), lazabemide (Ro 19 6327), described in Ann. Neurol, 40(1): 99-107 (1996), and SL25.1 131, described in Aubin et al., J. Pharmacol. Exp. Ther., 310: 1171-1 182 (2004).

[0229] In additional embodiments, the monoamine modulator is an "uptake inhibitor," which increases extracellular monoamine levels by inhibiting the transport of monoamines away from the synaptic cleft and/or other extracellular regions. In some embodiments, the monoamine modulator is a monoamine uptake inhibitor, which may selectively/preferentially inhibit uptake of one or more monoamines relative to one or more other monoamines. The term "uptake inhibitors" includes compounds that inhibit the transport of monoamines (e.g., uptake inhibitors) and/or the binding of monoamine substrates (e.g., uptake blockers) by transporter proteins (e.g., the dopamine transporter (DAT), the NE transporter (NET), the 5-HT transporter (SERT), and/or the extraneuronal monoamine transporter (EMT)) and/or other molecules that mediate the removal of extracellular monoamines. Monoamine uptake inhibitors are generally classified according to their potencies with respect to particular monoamines, as described, e.g., in Koe, J. Pharmacol. Exp. Ther. 199: 649-661 (1976). However, references to compounds as being active against one or more monoamines are not intended to be exhaustive or inclusive of the monoamines modulated in vivo, but rather as
general guidance for the skilled practitioner in selecting compounds for use in therapeutic methods provided herein.

[0230] In embodiments relating to a biogenic amine modulator used in a combination or method as disclosed herein, the modulator may be (i) a norepinephrine and dopamine reuptake inhibitor, such as bupropion (described, e.g., in U.S. Pat. 3,819,706 and 3,885,046), or (S,S)-hydroxybupropion (described, e.g., in U.S. Pat. 6,342,496); (ii) selective dopamine reuptake inhibitors, such as medifoxamine, amineptine (described, e.g., in U.S. Pat. 3,758,528 and 3,821,249), GBR12909, GBR12783 and GBR13069, described in Andersen, Eur J Pharmacol, 166:493-504 (1989); or (iii) a monoamine "releaser" which stimulates the release of monoamines, such as biogenic amines from presynaptic sites, e.g., by modulating presynaptic receptors (e.g., autoreceptors, heteroreceptors), modulating the packaging (e.g., vesicular formation) and/or release (e.g., vesicular fusion and release) of monoamines, and/or otherwise modulating monoamine release. Advantageously, monoamine releasers provide a method for increasing levels of one or more monoamines within the synaptic cleft or other extracellular region independently of the activity of the presynaptic neuron.

[0231] Monoamine releasers useful in combinations provided herein include fenfluramine or p-chloroamphetamine (PCA) or the dopamine, norepinephrine, and serotonin releasing compound amineptine (described, e.g., in U.S. Pat. 3,758,528 and 3,821,249).

Phosphodiesterase (PDE) Agents

[0232] In certain embodiments, one or more phosphodiesterase (PDE) antagonist agents are useful in combination with a first neurogenic agent of the present invention. Non-limiting examples of PDE agents as known to the skilled person and useful herein include the following.

[0233] In some embodiments, a reported inhibitor of PDE activity include an inhibitor of a cAMP-specific PDE. Non-limiting examples of cAMP specific PDE inhibitors useful in the methods described herein include a pyrroldinone, such as a compound disclosed in U.S. Pat. 5,665,754, US20040152754 or US20040023945; a quinazolineone, such as a compound disclosed in U.S. Pat. 6,747,035 or 6,828,315, WO 97/49702 or WO 97/42174; a xanthine derivative; a phenylpyridine, such as a compound disclosed in U.S. Pat. 6,410,547 or 6,090,817, or WO 97/22585; a diazepine derivative, such as a compound disclosed in WO 97/36905; an oxime derivative, such as a compound disclosed in U.S. Pat. 5,693,659 or WO
96/00215; a naphthyridine, such as a compound described in U.S. Pats. 5,817,670, 6,740,662, 6,136,821, 6,331,548, 6,297,248, 6,541,480, 6,642,250, or 6,900,205, or Trifilieff et al., *Pharmacology*, 301(1): 241-248 (2002), or Hersperger et al., *J Med Chem.*, 43(4):675-82 (2000); a benzo furan, such as a compound disclosed in U.S. Pats. 5,902,824, 6,211,120, 6,514,996, 6,716,987, 6,376,535, 6,080,782, or 6,054,475, or EP 819688, EP685479, or Perrier et al., *Bioorg. Med. Chem. Lett.* 9:323-326 (1999); a phenan thridine, such as that disclosed in U.S. Pats. 6,191,138, 6,127,378, or 6,127,378; a benzoxazole, such as that disclosed in U.S. Pat. 6,166,041 or 6,376,485; a purine derivative, such as a compound disclosed in U.S. Pat. 6,228,859; a benzamide, such as a compound described in U.S. Pat. 5,981,527 or 5,712,298, or WO95/01338, WO 97/48697 or Ashton et al., *J. Med Chem* 37: 1696-1703 (1994); a substituted phenyl compound, such as a compound disclosed in U.S. Pats. 6,297,264, 5,866,593,65 5,859,034, 6,245,774, 6,197,792, 6,080,790, 6,077,854, 5,962,483, 5,674,880, 5,786,354, 5,739,144, 5,776,958, 5,798,373, 5,891,896, 5,849,770, 5,550,137, 5,340,827, 5,780,478, 5,780,477, or 5,633,257, or WO 95/35283; a substituted biphenyl compound, such as that disclosed in U.S. Pat. 5,877,190; or a quinilinone, such as a compound described in U.S. Pat. 6,800,625 or WO 98/14432.

[0234] Additional non-limiting examples of reported cAMP-specific PDE inhibitors useful in methods disclosed herein include a compound disclosed in U.S. Pats. 6,818,651, 6,737,436, 6,613,778, 6,617,357, 6,146,876, 6,838,559, 6,884,800, 6,716,987, 6,514,996, 6,376,535, 6,740,655, 6,559,168, 6,069,151, 6,365,585, 6,313,116, 6,245,774, 6,01,1037, 6,127,363, 6,303,789, 6,316,472, 6,348,602, 6,331,543, 6,333,354, 5,491,147, 5,608,070, 5,622,977, 5,580,888, 6,680,336, 6,569,890, 6,569,885, 6,500,856, 6,486,186, 6,458,787, 6,455,562, 6,444,671, 6,423,710, 6,376,489, 6,372,777, 6,362,213, 6,313,156, 6,294,561, 6,258,843, 6,258,833, 6,121,279, 6,043,263, RE38,624, 6,297,257, 6,251,923, 6,613,794, 6,407,108, 6,107,295, 6,103,718, 6,479,494, 6,602,890, 6,545,158, 6,545,025, 6,498,160, 6,743,802, 6,787,554, 6,828,333, 6,869,945, 6,894,041, 6,924,292, 6,949,573, 6,953,810, 6,156,753, 5,972,927, 5,962,492, 5,814,651, 5,723,460, 5,716,967, 5,686,434, 5,502,072, 5,116,837, 5,091,431; 4,670,434; 4,490,317; 5,710,160, 5,710,170, 6,384,236, or 3,941,785, or US200501 19225, US20050026913, US20050059686, US20040138279, US20050222128, US20040214843, US200400 106631, US 20030045557, U S 20020198198, US20030162802, US20030092908, US 20030104974, US20030105071, 20030092746, US20050148604, W O 99/65880, W O 00/26201, W O 98/06704, W O 00/59890, WO907704, WO9422852, W O 98/20007, W O 02/096423, W O 98/18796, W O 98/02440, W O 02/096463, W O 97/44337,

[0235] In some embodiments, the reported cAMP-specific PDE inhibitor is Cilomilast (SB-207499); Filaminast; Tibenelast (LY-186655); Ibudilast; Piclamilast (RP 73401);
Doxofylline; Cipamfylline (HEP-688); atizoram (CP-80633); theophylline;
isobutylmethylxanthine; Mesopram (ZK-1 17137); Zardaverine; vinpocetine; Rolipram (ZK-6271 1); Arofylline (LAS-31025); roflumilast (BY-217); Pumafentrin (BY-343);
Denbufylline; EHNA; milrinone; Siguazodan; Zaprinast; Tolafentrine; Isbufylline; IBMX;
IC-485; dyphylline; verophylline; bamifylline; pentoxyfilline; enprofylline; lirilimilast (BAY 19-8004); filaminast (WAY- PDA-641); benafentrine; trequinsin; nitroquazone; cilostamide;
vesnarinone; piroximone; enoximone; amrinone; olprinone; imazodan or 5-methyl-imazodan;
indolidan; anagrelide; carbazeran; amipzone; emoradan; motapizone; phthalazinol; lixazinone (RS 82856); quazinone; bemorandan (RWJ 22867); adibendan (BM 14,478); Pimobendan
(MCI-1 54); Saterinone (BDF 8634); Tetomilast (OPC-6535); benzafentrine; sulmazole (ARL
115); Revizinone; 349-U-85; AH-21-132; ATZ-1993; AWD-12-343; AWD-12-281; AWD-
12-232; BRL 50481; CC-7085; CDC-801; CDC-998; CDP-840; CH-422; CH-673; CH-928;
CH-3697; CH-3442; CH-2874; CH-4139; Chiroscience 245412; CI-930; CI-1018; CI-1044;
CI-1 118; CP-353164; CP-77059; CP-146523; CP-293321; CP-220629; CT-2450; CT-2820;
CT-3883; CT-5210; D-4418; D-22888; E-4021; EMD 54622; EMD-53998; EMD-57033;
GF-248; GW-3600; IC-485; ICI 63197; ICI 153,1 10; IPL-4088; KF-19514; KW-4490; L-
787258; L-826141; L-791943; LY181512; NCS-613; NM-702; NSP-153; NSP-306; NSP-
307; Org-30029; Org-20241; Org-9731; ORG 9935; PD-168787; PD-190749; PD-190036;
PDB-093; PLX650; PLX369; PLX371; PLX788; PLX939; Ro-20-1724; RPR-132294; RPR-
117658A; RPR-1 14597; RPR-122818; RPR-132703; RS-17597; RS-25344; RS-14203; SCA
40; Sch-351591; SDZ-ISQ-844; SDZ-MKS-492; SKF 94120; SKF-95654; SKF-107806;
SKF 96231; T-440; T-2585; WAY-126120; WAY-122331; WAY-127093B; WIN-63291;
WIN-62582; V-1 1294A; VMX 554; VMX 565; XT-044; XT-61 1; Y-590; YM-58897; YM-
976; ZK-62711; methyl 3-[6-(2H-3,4,5-tetrahydropyran-2-yl)oxy]-2-(3-
thienylcarbonyl)benzo[b]furan-3-yl)propanoate; 4-[4-methoxy-3-(5-
phenylpentoxy)phenyl]-2-methylbenzoic acid; methyl 3-[2-[(4-chlorophenyl)carbonyl]-6-
hydroxybenzo [b]furan-3-yl)propanoate ; (R *,R *)-(-) -methyl 13-acetyl-4- [3-(cycloproxyloxy)-
4-methoxyphenyl]-3-methyl-1-pyrrolidinecarboxylate; or 4-(3-bromophenyl)-1-ethyl-7-methylhydropyridino[2,3-b]pyridin-2-one.

[0236] In some embodiments, the reported PDE inhibitor inhibits a cGMP-specific PDE. Non-limiting examples of a cGMP specific PDE inhibitor for use in the combinations and methods described herein include a pyrimidine or pyrimidinone derivative, such as a compound described in U.S. Pats. 6677335, 6458951, 6251904, 6787548, 5294612, 5250534, or 6469012, WO 94/28902, WO96/16657, EP0702555, and Eddahibi, Br. J. Pharmacol., 125(4): 681-688 (1988); a griseolic acid derivative, such as a compound disclosed in U.S. Pat. 4,460,765; a 1-arylnaphthalene lignan, such as that described in Ukita, J. Med. Chem. 42(7): 1293-1305 (1999); a quinazoline derivative, such as 4-[[3',4'-(methyleneoxy)benzyl]amino]-6-methoxyquinazoline) or a compound described in U.S. Pats. 3,932,407 or 4,146,718, or RE3 1,617; a pyrroloquinolone or pyrrolopyridinone, such as that described in U.S. Pat. 6,686,349, 6,635,638, 6,818,646, US200501 13402; a carboline derivative, such a compound described in U.S. Pats. 6,492,358, 6,462,047, 6,821,975, 6,306,870, 6,117,881, 6,043,252, or 3,819,631, US20030166641, WO 97/43287, Daugan et al, J Med Chem., 46(21):4533-42 (2003), or Daugan et al., J Med Chem., 9;46(21):4525-32 (2003); an imidazo derivative, such as a compound disclosed in U.S. Pats. 6,130,333, 6,566,360, 6,362,178, or 6,582,351, US20050070541, or US20040067945; or a compound described in U.S. Pats. 6,825,197, 5,719,283, 6,943,166, 5,981,527, 6,576,644, 5,859,009, 6,943,253, 6,864,253, 5,869,516, 5,488,055, 6,140,329, 5,859,006, or 6,143,777, WO 96/16644, WO 01/19802, WO 96/26940, Dunn, Ore. Proc. Res. Dev., 9: 88-97 (2005), or Bi et al., Bioorg Med Chem Lett, 11(18):2461-4 (2001).

[0237] In some embodiments, the PDE inhibitor used in a combination or method disclosed herein is caffeine. In other embodiments, the caffeine is administered simultaneously with the first neurogenic agent. In alternative embodiments, the caffeine is administered in a formulation, dosage, or concentration lower or higher than that of a caffeinated beverage such as coffee, tea, or soft drinks. In further embodiments, the caffeine is administered by a nonoral means, including, but not limited to, parenteral (e.g., intravenous, intradermal, subcutaneous, inhalation), transdermal (topical), transmucosal, rectal, or intranasal (including, but not limited to, inhalation of aerosol suspensions for delivery of compositions to the nasal mucosa, trachea and bronchioli) administration. The disclosure includes embodiments with the explicit exclusion of caffeine or another one or more of the described agents for use in combination with the first neurogenic agent.
In further alternative embodiments, the caffeine is in an isolated form, such as that which is separated from one or more molecules or macromolecules normally found with caffeine before use in a combination or method as disclosed herein. In other embodiments, the caffeine is completely or partially purified from one or more molecules or macromolecules normally found with the caffeine. Exemplary cases of molecules or macromolecules found with caffeine include a plant or plant part, an animal or animal part, and a food or beverage product.

Non-limiting examples of a reported PDE1 inhibitor include IBMX; vinpocetine; MMPX; KS-505a; SCH-51866; W-7; PLX650; PLX371; PLX788; a phenothiazines; or a compound described in U.S. Pat. 4,861,891.

Non-limiting examples of a PDE2 inhibitor include EHNA; PLX650; PLX369; PLX788; PLX 939; Bay 60-7550 or a related compound described in Boess et al, Neuropharmacology, 47(7): 1081-92 (2004); or a compound described in US20020 132754.

Non-limiting examples of reported PDE3 inhibitors include a dihydroquinolinone compound such as cilostamide, cilostazol, vesnarinone, or OPC 3911; an imidazoline such as piroximine or enoximone; a bipyridine such as milrinone, amrinone or olprinone; an imidazoline such as imazodon or 5-methyl-imazodon; a pyridazine such as indolidan; LY1 815 12 (see Komas et al. "Differential sensitivity to cardiotonic drugs of cyclic AMP phosphodiesterases isolated from canine ventricular and sinoatrial-enriched tissues." J Cardiovasc Pharmacol., 1989 14(2):213-20); ibudilast; isomazole; motapizone; phthalazinol; treqinsin; lixazinone (RS 82856); Y-590; SKF 94120; quazinone; ICI 153,110; bemorandan (RWJ 22867); siguazodan (SK&F 94836); adibendan (BM 14,478); Pimobendan (UD-CG 115, MCI-154); Saterinone (BDF 8634); NSP-153; zardaverine; a quinazolone; benzafentrine; sulmazol (ARL 115); ORG 9935; CI-930; SKF-95654; SDZ-MKS-492; 349-U-85; EMD-53998; EMD-57033; NSP-306; NSP-307; Revizinone; NM-702; WIN-62582; ATZ-1993; WIN-63291; ZK-6271; PLX650; PLX369; PLX788; PLX939; anagrelide; carbazeran; ampizone; emoradan; or a compound disclosed in 6,156,753.

Non-limiting examples of reported PDE4 inhibitors include a pyrrolidinone, such as a compound disclosed in U.S. Pat. 5,665,754, US200401 52754 or US20040023945; a quinazolineone, such as a compound disclosed in U.S. Pats. 6,747,035 or 6,828,315, WO 97/49702 or WO 97/42174; a xanthine derivative; a phenylpyridine, such as a compound disclosed in U.S. Pat. 6,410,547 or 6,090,817 or WO 97/22585; a diazepine derivative, such
as a compound disclosed in WO 97/36905; an oxime derivative, such as a compound described in U.S. Pat. 5,693,659 or WO 96/00215; a naphthrydine, such as a compound disclosed in U.S. Pats. 5,817,670, 6,740,662, 6,136,821, 6,331,548, 6,297,248, 6,541,480, 6,642,250, or 6,900,205, Trifiliieff et al., Pharmacology, 301(1): 241-248 (2002) or Hersperger et al., J Med Chem., 43(4):675-82 (2000); a benzofuran, such as a compound disclosed in U.S. Pats. 5,902,824, 6,211,203, 6,514,996, 6,716,987, 6,376,535, 6,080,782, or 6,054,475, EP 819688, EP685479, or Perrier et al., Bioorg. Med. Chem. Lett, 9:323-326 (1999); a phenanthridine, such as that disclosed in U.S. Pats. 6,191,138, 6,121,279, or 6,127,378; a benzoxazole, such as that disclosed in U.S. Pats. 6,166,041 or 6,376,485; a purine derivative, such as a compound disclosed in U.S. Pat. 6,228,859; a benzamide, such as a compound described in U.S. Pats. 5,981,527 or 5,712,298, WO95/01388, WO 97/48697, or Ashton et al., J. Med Chem. 37: 1696-1703 (1994); a substituted phenyl compound, such as a compound disclosed in U.S. Pats. 6,297,264, 5,866,593,65 5,859,034, 6,245,774, 6,197,792, 6,080,790, 6,077,854, 5,962,483, 5,674,880, 5,786,354, 5,739,144, 5,776,958, 5,798,373, 5,891,896, 5,849,770, 5,550,137, 5,340,827, 5,780,478, 5,780,477, or 5,633,257, or WO 95/35283; a substituted biphenyl compound, such as that disclosed in U.S. Pat. 5,877,190; or a quinilinone, such as a compound described in U.S. Pat. 6,800,625 or WO 98/14432.

In some embodiments, the reported PDE4 inhibitor is Cilomilast (SB-207499); Filaminast; Tibenelast (LY-186655); Ibudilast; Picamilast (RP 73401); Doxofylline; Cipamfylline (HEP-688); atizoram (CP-80633); theophylline; isobutylmethylxanthine; Mesopram (ZK-1 17137); Zardaverine; vinpocetine; Rolipram (ZK-6271 1); Arofylline (LAS-31025); roflumilast (BY-2 17); Pumafentrin (BY-343); Denbufylline; EHNA; milrinone; Siguazodan; Zaprinast; Tolafentrine; Isbufylline; IBMX; IC-485; dyphylline; verolylline; bamifylline; pentoxyfilline; enprofilline; lirilmilast (BAY 19-8004); filaminast (WAY- PDA-641); benafentrine; trequinsin; nitroquazone; Tetomilast (OPC-6535); Arofylline (LAS-31025); roflumilast (BY-2 17); Pumafentrin (BY-343); Denbufylline; EHNA; milrinone; Siguazodan; Zaprinast; Tolafentrine; Isbufylline; IBMX; IC-485; dyphylline; verolylline; bamifylline; pentoxyfilline; enprofilline; lirilmilast (BAY 19-8004); filaminast (WAY- PDA-641); benafentrine; trequinsin; nitroquazone; Tetomilast (OPC-6535); Arofylline (LAS-31025); roflumilast (BY-2 17); Pumafentrin (BY-343); Denbufylline; EHNA; milrinone; Siguazodan; Zaprinast; Tolafentrine; Isbufylline; IBMX; IC-485; dyphylline; verolylline; bamifylline; pentoxyfilline; enprofilline; lirilmilast (BAY 19-8004); filaminast (WAY- PDA-641); benafentrine; trequinsin; nitroquazone; Tetomilast (OPC-6535); Arofylline (LAS-31025); roflumilast (BY-2 17); Pumafentrin (BY-343); Denbufylline; EHNA; milrinone; Siguazodan; Zaprinast; Tolafentrine; Isbufylline; IBMX; IC-485; dyphylline; verolylline; bamifylline; pentoxyfilline; enprofilline; lirilmilast (BAY 19-8004); filaminast (WAY- PDA-641); benafentrine; trequinsin; nitroquazone; Tetomilast (OPC-6535); Arofylline (LAS-31025); roflumilast (BY-2 17); Pumafentrin (BY-343); Denbufylline; EHNA; milrinone; Siguazodan; Zaprinast; Tolafentrine; Isbufylline; IBMX; IC-485; dyphylline; verolylline; bamifylline; pentoxyfilline; enprofilline; lirilmilast (BAY 19-8004); filaminast (WAY- PDA-641); benafentrine; trequinsin; nitroquazone; Tetomilast (OPC-6535); Arofylline (LAS-31025); roflumilast (BY-2 17); Pumafentrin (BY-343); Denbufylline; EHNA; milrinone; Siguazodan; Zaprinast; Tolafentrine; Isbufylline; IBMX; IC-485; dyphylline; verolylline; bamifylline; pentoxyfilline; enprofilline; lirilmilast (BAY 19-8004); filaminast (WAY- PDA-641); benafentrine; trequinsin; nitroquazone; Tetomilast (OPC-6535); Arofylline (LAS-31025); roflumilast (BY-2 17); Pumafentrin (BY-343); Denbufylline; EHNA; milrinone; Siguazodan; Zaprinast; Tolafentrine; Isbufylline; IBMX; IC-485; dyphylline; verolylline; bamifylline; pentoxyfilline; enprofilline; lirilmilast (BAY 19-8004); filaminast (WAY- PDA-641); benafentrine; trequinsin; nitroquazone; Tetomilast (OPC-6535); Arofylline (LAS-31025); roflumilast (BY-2 17); Pumafentrin (BY-343); Denbufylline; EHNA; milrinone; Siguazodan; Zaprinast; Tolafetrin
as that described in U.S. Pats. 6,686,349, 6,635,638, or 6,818,646, US200501 13402; a
carboline derivative, such a compound described in U.S. Pats. 6,492,358, 6,462,047,
6,821,975, 6,306,870, 6.1 17,881, 6,043,252, or 3,819,631, US20030166641, WO 97/43287,
Daugan et al., J Med Chem., 46(21):4533-42 (2003), and Daugan et al., J Med Chem.,
9;46(21):4525-32 (2003); an imidazo derivative, such as a compound disclosed in U.S. Pats.
6,130,333, 6,566,360, 6,362,178, or 6,582,351, US20050070541, or US20040067945; or a
compound described in U.S. Pats. 6,825,197, 6,943,166, 5,981,527, 6,576,644, 5,859,009,
6,943,253, 6,864,253, 5,869,516, 5,488,055, 6,140,329, 5,859,006, or 6,143,777, WO

[0246] In some embodiments, a reported PDE5 inhibitor is zaprinast; MY-5445;
dipyridamole; vinpocetine; FR229934; 1-methyl-3-isobutyl-8-(methylamino)xanthine;
furazlocillin; Sch-51866; E4021; GF-196960; IC-351; T-1032; sildenafil; tadalafil;
vardenafil; DMPPO; RX-RA-69; KT-734; SKF-96231; ER-21355; BF/GP-385; NM-702;
PLX650; PLX1 34; PLX369; PLX788; or vesnarinone.

[0247] In some embodiments, the reported PDE5 inhibitor is sildenafil or a related
compound disclosed in U.S. Pats. 5,346,901, 5,250,534, or 6,469,012; tadalafil or a related
compound disclosed in U.S. Pat. 5,859,006, 6,140,329, 6,821,975, or 6,943,166; or vardenafil
or a related compound disclosed in U.S. Pat. 6,362,178.

[0248] Non-limiting examples of a reported PDE6 inhibitor useful in a combination or
method described herein include dipyridamole or zaprinast.

[0249] Non-limiting examples of a reported PDE7 inhibitor for use in the combinations and
methods described herein include BRL 50481; PLX369; PLX788; or a compound described
in U.S. Pats. 6,818,651; 6,737,436, 6,613,778, 6,617,357; 6,146,876, 6,838,559, or 6,884,800,
US20050059686; US20040138279; US20050222138; US20040214843; US200401 06631;
US20030100571; 20030092721; or US20050148604.

[0250] A non-limiting examples of a reported inhibitor of PDE8 activity is dipyridamole.

[0251] Non-limiting examples of a reported PDE9 inhibitor useful in a combination or
method described herein include SCH-51866; IBMX; or BAY 73-6691.
Non-limiting examples of a PDE 10 inhibitor include sildenafil; SCH-5 1866; papaverine; Zaprinast; Dipyridamole; E4021; Vinpocetine; EHNA; Milrinone; Rolipram; PLX107; or a compound described in U.S. Pat. 6,930,14 US20040138249, or US20040249148.

Non-limiting examples of a PDE11 inhibitor includes IC-35 1 or a related compound described in WO 9519978; E4021 or a related compound described in WO 9307124; UK-235,187 or a related compound described in EP 579496; PLX788; Zaprinast; Dipyridamole; or a compound described in US20040 10663 1 or Maw et al., Bioorg Med Chem Lett. 2003 Apr 17;13(8):1425-8.


In some embodiments, the reported PDE inhibitor inhibits dual-specificity PDE. Non-limiting examples of a dual-specificity PDE inhibitor useful in a combination or method described herein include a cAMP-specific or cGMP-specific PDE inhibitor described herein; MMPX; KS-505a; W-7; a phenothiazine; Bay 60-7550 or a related compound described in Boess et al., Neuropharmacology, 47(7): 1081-92 (2004); UK-235,187 or a related compound described in EP 579496; or a compound described in U.S. Pats. 6,930,14 or 4,861,891, US20020 132754, US20040138249, US20040249148, US20040 106631, WO 951997, or Maw et al., Bioorg Med Chem Lett. 2003 Apr 17;13(8):1425-8.

In some embodiments, a reported PDE inhibitor exhibits dual-selectivity, being substantially more active against two PDE isozymes relative to other PDE isozymes. For example, in some embodiments, a reported PDE inhibitor is a dual PDE4/PDE7 inhibitor, such as a compound described in US20030 104974; a dual PDE3/PDE4 inhibitor, such as zardavemine, tolafentrine, benafentrine, trequinsine, Org-30029, L-686398, SDZ-ISQ-844, Org-20241, EMD-54622, or a compound described in U.S. Pats. 5,521,187, or 6,306,869; or a dual PDE1/PDE4 inhibitor, such as KF19514 (5-phenyl-3-(3-pyridyl)methyl-3H-imidazo[4,5-c] [1,8]naphthyridin-4 (5H)-one).
Neurosteroid Agents

[0257] In certain embodiments, one or more neurosteroid agents are useful in combination with a first neurogenic agent of the present invention. Non-limiting examples of neurosteroid agents as known to the skilled person and useful herein include pregnenolone and allopregnenalone.

NSAID Agents

[0258] In certain embodiments, one or more non-steroidal anti-inflammatory drug (NSAID) agents are useful in combination with a first neurogenic agent of the present invention. Non-limiting examples of NSAID agents as known to the skilled person and useful herein include the following.

[0259] Non-limiting examples of a reported NSAID include a cyclooxygenase inhibitor, such as indomethacin, ibuprofen, celecoxib, coxcetacin, naproxen, or aspirin. Additional non-limiting examples for use in combination with a first neurogenic agent include rofecoxib, meloxicam, piroxicam, valdecoxb, parecoxib, etorcixib, etodolac, nimesulide, acemetacin, bufexamac, diflunisal, ethenamide, etofenamate, flubufen, isoxicam, kebuzone, lonazolac, meclofenamic acid, metamizol, mofebutazone, niiflumic acid, oxyphenbutazone, paracetamol, phenidone, propacetamol, propyphenazone, salicylamide, tenoxicam, tiaprofenic acid, oxaprin, lornoxicam, nabumetone, minocycline, benorylate, aloxiprin, salsalate, flurbiprofen, ketoprofen, fenoprofen, fenbufen, benoxaprofen, suprofen, piroxicam, meloxicam, diclofenac, ketorolac, fenbutofen, sulindac, tolmetin, xyphenbutazone, phenylbutazone, feprazone, azapropazone, flufenamic acid or mefenamic acid.

Anti-Migraine Agents

[0260] In certain embodiments, one or more anti-migraine agents are useful in combination with a first neurogenic agent of the present invention. Non-limiting examples of anti-migraine agents as known to the skilled person and useful herein include the following.

[0261] Non-limiting examples of anti-migraine agents include a triptan, such as almotriptan or almotriptan malate; naratriptan or naratriptan hydrochloride; rizatriptan or rizatriptan benzoate; sumatriptan or sumatriptan succinate; zolmitriptan or zolmitriptan, frovatriptan or frovatriptan succinate; or eletriptan or eletriptan hydrobromide. Embodiments of the

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disclosure may exclude combinations of triptans and an SSRI or SNRI that result in life threatening serotonin syndrome.

[0262] Other non-limiting examples include an ergot derivative, such as dihydroergotamine or dihydroergotamine mesylate, ergotamine or ergotamine tartrate; diclofenac or diclofenac potassium or diclofenac sodium; flurbiprofen; amitriptyline; nortriptyline; divalproex or divalproex sodium; propranolol or propranolol hydrochloride; verapamil; methysergide (CAS RN 361-37-5); metoclopramide; prochlorperazine (CAS RN 58-38-8); acetaminophen; topiramate; GW274150 ([2-[(l-iminoethyl) amino]ethyl]-L-homocysteine); or ganaxalone (CAS RN 38398-32-2).

[0263] Additional non-limiting examples include a COX-2 inhibitor, such as Celecoxib.

**Nuclear Hormone Receptor Agents**

[0264] In certain embodiments, one or more nuclear hormone receptor modulatory agents are useful in combination with a first neurogenic agent of the present invention. Non-limiting examples of such agents as known to the skilled person and useful herein include the following.

[0265] Without being bound to theory, nuclear hormone receptors are activated via ligand interactions to regulate gene expression, in some cases as part of cell signaling pathways. Non-limiting examples of a reported modulator include a dihydrotestosterone agonist such as dihydrotestosterone; a 2-quinolone like LG121071 (4-ethyl-1,2,3,4-tetrahydro-6-(trifluoromethyl)-8-pyridon0[5,6-g] quinoline); a non-steroidal agonist or partial agonist compound described in U.S. Pat. No.6,017,924; LGD2226 (see WO 01/16108, WO 01/16133, WO 01/16139, and Rosen et al. "Novel, non-steroidal, selective androgen receptor modulators (SARMs) with anabolic activity in bone and muscle and improved safety profile." J Musculoskeletal Neuronal Interact. 2002 2(3):222-4); or LGD294 1 (from collaboration between Ligand Pharmaceuticals Inc. and TAP Pharmaceutical Products Inc.).

[0266] Additional non-limiting examples of a reported modulator include a selective androgen receptor modulator (SARM) such as andarine, ostarine, prostarin, or andromustine (all from GTx, Inc.); bicalutamide or a bicalutamide derivative such as GTx-007 (U.S. Pat. 6,492,554); or a SARM as described in U.S. Pat. 6,492,554.
Further non-limiting examples of a reported modulator include an androgen receptor antagonist such as cyproterone, bicalutamide, flutamide, or nilutamide; a 2-quinolone such as LG120907, represented by the following structure:

![Structure of LG120907]

or a derivative compound represented by the following structure:

![Structure of derivative compound]

(see Allan et al. "Therapeutic androgen receptor ligands" Nucl Recept Signal 2003; 1:e009); a phthalamide, such as a modulator as described by Miyachi et al. ("Potent novel nonsteroidal androgen antagonists with a phthalimide skeleton." Bioorg. Med. Chem. Lett. 1997 7:1483—1488); osaterone or osaterone acetate; hydroxyflutamide; or a non-steroidal antagonist described in U.S. Pat. No.6,017,924.

Other non-limiting examples of a reported modulator include a retinoic acid receptor agonist such as all-trans retinoic acid (Tretinoin); isotretinoin (13-cis-retinoic acid); 9-cis retinoic acid; bexarotene; TAC-101 (4-[3,5-bis(trimethylsilyl) benzamide] benzoic acid); AC-261066 (see Lund et al. "Discovery of a potent, orally available, and isoform-selective retinoic acid beta2 receptor agonist." J Med Chem. 2005 48(24):7517-9); LGD1550 ((2E,4E,6E)-3-methyl-7-(3,5-di-ter-butylphen-yl)octatrienoic acid); E6060 (E6060 [4-{5-[7-fluoro-4-(trifluoromethyl)benzo[b]furan-2-yl]-IH-2-pyrrolyl]benzoic acid]; agonist 1 or 2 as described by Schapira et al. ("In silico discovery of novel Retinoic Acid Receptor agonist structures." BMC Struct Biol. 2001; 1:1 (published online 2001 June 4) where "Agonist 1 was purchased from Bionet Research (catalog number 1G-4335). Agonist 2 was purchased from Sigma-Aldrich (Sigma Aldrich library of rare chemicals. Catalog number S08503-1"); a synthetic acetylenic retinoic acid, such as AGN 190121 (CAS RN: 132032-67-8), AGN 190168 (or Tazarotene or CAS RN 118292-40-3), or its metabolite AGN 190299 (CAS RN 118292-41-4); Etretinate; acitretin; an acetylenic retinoate, such as AGN 190073 (CAS 132032-68-9), or AGN 190089 (or 3-Pyridinecarboxylic acid, 6-(4-(2,6,6-trimethyl-
cyclohexen-1-yl)-3-buten-1-ylnyl)-, ethyl ester or CAS RN 116627-73-7). In further embodiments, the modulator is selected from one or more of thyroxin, tri-iodothyronine, or levothyroxine.


Furthermore, the additional agent may be a reported Cortisol receptor modulator, such as methylprednisolone or its prodrug methylprednisolone suleptanate; PI-1020 (NCX-1020 or budesonide-21-nitrooxymethylbenzoate); fluticasone furoate; GW-215864; betamethasone valerate; beclomethasone; prednisolone; or BVT-3498 (AMG-311).

Alternatively, the additional agent may be a reported aldosterone (or mineralocorticoid) receptor modulator, such as spironolactone or eplerenone.

In other embodiments, the additional agent may be a reported progesterone receptor modulator such as Asoprisnil (CAS RN 199396-76-4); mesopregestin or J1042; J956; medroxyprogesterone acetate (MPA); R5020; tanaproget; trimegestone; progesterone; norgestomet; melengestrol acetate; mifepristone; onapristone; ZK1 373 16; ZK23021 1 (see Fuhrmann et al. "Synthesis and biological activity of a novel, highly potent progesterone receptor antagonist." J Med Chem. 2000 43(26):5010-6); or a compound described in Spitz "Progesterone antagonists and progesterone receptor modulators: an overview." Steroids 2003 68(10-13):981-93.

In certain alternative embodiments, the additional agent may be a reported i) peroxisome proliferator-activated receptor (PPAR) agonist such as muraqlitazar; tesaglitazar; reglitazar; GW-409544 (see Xu et al. "Structural determinants of ligand binding selectivity between the peroxisome proliferator-activated receptors." PNAS U S A. 2001 98(24): 13919-
24); or DRL 11605 (Dr. Reddy's Laboratories); ii) a peroxisome proliferator-activated receptor alpha agonist like clofibrate; ciprofibrate; fenofibrate; gemfibrozil; DRF-10945 (Dr. Reddy's Laboratories); iii) a peroxisome proliferator-activated receptor delta agonist such as GW501516 (CAS RN 317318-70-0); and/or iv) a peroxisome proliferator-activated gamma receptor agonist like a hydroxyocta decadienoic acid (HODE); a prostaglandin derivatives, such as 15-deoxy-Deltal2,14-prostaglandin J2; a thiazolidinedione (glitazone), such as pioglitazone, troglitazone; rosiglitazone maleate; ciglitazone; Balaglitazone or DRF-2593; AMG 131 (from Amgen); or G1262570 (from Glaxo Wellcome) (such that more than one PPAR modulating agent is used in combination, in certain embodiments). In additional embodiments, a PPAR ligand is a PPARγ antagonist such as T0070907 (CAS RN 313516-66-4) or GW9662 (CAS RN 22978-25-2).

[0274] In additional embodiments, the additional agent may be a reported modulator of an "orphan" nuclear hormone receptor. Embodiments include a reported modulator of a liver X receptor, such as a compound described in U.S. Pat. 6,924,311; a farnesoid X receptor, such as GW4064 as described by Maloney et al. ("Identification of a chemical tool for the orphan nuclear receptor FXR." J Med Chem. 2000 43(16):2971-4); a RXR receptor; a CAR receptor, such as 1,4-bis[2-(3,5-dichloropyridyloxy)] benzene (TCPOBOP); or a PXR receptor, such as SR-12813 (tetra-ethyl 2-(3,5-di-tert-butyl-4-hydroxyphenyl)ethenyl-1,1-bisphosphonate).

[0275] In additional embodiments, the agent in combination is ethyl eicosapentaenoate or ethyl-EPA (also known as 5,8,11,14,17-eicosapentaenoic acid ethyl ester or miraxion, CAS RN 86227-47-6), docosahexaenoic acid (DHA), or a retinoid acid drug. As an additional non-limiting example, the agent may be Omacor, a combination of DHA and EPA, or idebenone (CAS RN 58186-27-9).

25 Nootropic Agents

[0276] In certain embodiments, one or more nootropic agents are useful in combination with a first neurogenic agent of the present invention. Non-limiting examples of nootropic agents as known to the skilled person and useful herein include the following.

[0277] Non-limiting examples of nootropic compounds include Piracetam (Nootropil), Aniracetam, Oxiracetam, Pramiracetam, Pyritinol (Enerbol), Ergoloid mesylates (Hydergine), Galantamine or Galantamine hydrobromide, Selegiline, Centropenoxine (Lucidril),
Desmopressin (DDAVP), Nicergoline, Vinpocetine, Picamilon, Vasopressin, Milacemide,
FK-960, FK-962, levetiracetam, nefiracetam, or hyperzine A (CAS RN: 102518-79-6).

Additional non-limiting examples of nootropic compounds include anapsos (CAS RN 75919-65-2), nebracetam (CAS RN 97205-34-0 or 116041-13-5), metrifonate, ensaculin (or CAS RN 155773-59-4 or KA-672) or ensaculin HCl, Rokan (CAS RN 122933-57-7 or EGB 761), AC-3933 (5-(3-methoxyphenyl)-3-(5-methyl-1,2,4-oxadiazol-3-yl)-2-oxo-1,2-dihydro-1,6-naphthyridine) or its hydroxylated metabolite SX-5745 (3-(5-hydroxymethyl-1,2,4-oxadiazol-3-yl)-5-(3-methoxyphenyl)-2-oxo-1,2-dihydro-1,6-naphthyridine), JTP-2942 (CAS RN 148152-77-6), sabeluzole (CAS RN 104383-17-7), ladostigil (CAS RN 209394-27-4), choline alphoscerate (CAS RN 28319-77-9 or Gliatilin), Dimebon (CAS RN 3613-73-8), tramiprosate (CAS RN 3687-18-1), omigapil (CAS RN 181296-84-4), cebaracetam (CAS RN 113957-09-8), fasoracetam (CAS RN 110958-19-5), PD-151832 (see Jaen et al. "In vitro and in vivo evaluation of the subtype-selective muscarinic agonist PD 151832." Life Sci. 1995 56(1 1-12):845-52), Vinconate (CAS RN 70704-03-9), PYM-50028 (Cogane) or PYM-50018 (Myogane) as described by Harvey ("Natural Products in Drug Discovery and Development. 27-28 June 2005, London, UK." iDrugs. 2005 8(9):719-21), SR-46559A (3-[[N-(2 diethyl-amino-2-methylpropyl)-6-phenyl-5'-propyl], dihydroergocristine (CAS RN 17479-19-5)), dabelotine (CAS RN 118976-38-8), zanapezil (CAS RN 142852-50-4).

Further non-limiting examples of nootropic agents include NBI-113 (from Neurocrine Biosciences, Inc.), NDD-094 (from Novartis), P-58 or P58 (from Pfizer), or SR-57667 (from Sanofi-Synthelabo).

**Nicotinic Receptor Agents**

In certain embodiments, one or more nicotinic receptor modulatory agents are useful in combination with a first neurogenic agent of the present invention. Non-limiting examples of nicotinic receptor agents as known to the skilled person and useful herein include the following.

Non-limiting examples of nicotinic receptor modulators include nicotine, acetylcholine, carbamylcholine, epibatidine, ABT-418 (structurally similar to nicotine, with an oxazol moiety replacing the pyridyl group of nicotine), epiboxidine (a structural analogue with elements of both epibatidine and ABT-418), ABT-594 (azetidine analogue of epibatidine), lobeline, SSR-591813, represented by the following formula:
In additional non-limiting embodiments for combination with a first neurogenic agent include one or more aromatase inhibitors. Reported aromatase inhibitors include, but are not limited to, nonsteroidal or steroidal agents. Non-limiting examples of the former, which inhibit aromatase via the heme prosthetic group, include anastrozole (Arimidex®), letrozole (Femara®), or vorozole (Rvisor). Non-limiting examples of steroidal aromatase inhibitors AIs, which inactivate aromatase, include, but are not limited to, exemestane (Aromasin®), androstanedione, or formestane (lentaron).

Additional non-limiting examples of aromatase for use in a combination or method as disclosed herein include aminoglutethimide, 4-androstene-3,6,17-trione (or “6-OXO”), or zoledronic acid or Zometa (CAS RN 118072-93-8).

Further non-limiting embodiments include a combination with a selective estrogen receptor modulator (SERM). Non-limiting examples include estradiol, tamoxifen, raloxifene, toremifene, clomifene, bazedoxifene, arzoxifene, or lasofoxifene. Additional non-limiting examples include a steroid antagonist or partial agonist, such as centchroman, clomiphene, or droloxifene.

**Cannabinoid Receptor Agents**

In certain embodiments, one or more cannabinoid receptor modulatory agents are useful in combination with a first neurogenic agent of the present invention. Non-limiting examples of cannabinoid receptor agents as known to the skilled person and useful herein include the following.

Non-limiting examples include synthetic cannabinoids, endogenous cannabinoids, or natural cannabinoids. In some embodiments, the reported cannabinoid receptor modulator is rimonabant (SR141716 or Acomplia), nabilone, levonantradol, marinol, or sativex (an extract containing both THC and CBD). Non-limiting examples of endogenous cannabinoids include arachidonylethanolamine (anandamide); analogs of anandamide, such as docosatetraenylethanolamine or homo-γ-linoenylethanolamide; N-acyl ethanolamine signalling lipids, such as the noncannabinimimetic palmitoylethanolamine or
oleoylethanolamine; or 2-arachidonyl glycerol. Non-limiting examples of natural cannabinoids include tetrahydrocannabinol (THC), cannabidiol (CBD), cannabinol (CBN), cannabigerol (CBG), cannabichromene (CBC), cannabicyclol (CBL), cannabivarol (CBV), tetrahydrocannabinvarin (THCV), cannabidivarin (CBDV), cannabichromevarin (CBCV), cannabigerovarin (CBGV), or cannabigerol monoethyl ether (CBGM).

**FAAH Antagonist Agents**

[0287] In certain embodiments, one or more fatty acid amide hydrolase (FAAH) inhibitory agents are useful in combination with a first neurogenic agent of the present invention. Non-limiting examples of FAAH inhibitory agents as known to the skilled person and useful herein include the following.

[0288] Non-limiting examples of reported FAAH inhibitor agents include URB597 (3’-carbamoyl-biphenyl-3-yl-cyclohexylcarbamate); CAY10401 (1-oxazolo[4,5-b]pyridin-2-yl-9-octadecynyl-one); OL-135 (1-oxo-[5-(2-pyridyl)-2-yl]-7-phenylheptane); anandamide (CAS RN 9442-68-8); AA-5-HT (see Bisogno et al. "Arachidonoylserotonin and other novel inhibitors of fatty acid amide hydrolase." Biochem Biophys Res Commun, 1998 248(3):515-22); 1-Octanesulfonfluryl fluoride; or 0-2142 or another arvanil derivative FAAH inhibitor as described by Di Marzo et al. ("A structure/activity relationship study on arvanil, an endocannabinoid and vanilloid hybrid." J Pharmacol Exp Ther. 2002 300(3):984-91).

Further non-limiting examples include SSR 411298 (from Sanofi-Aventis), JNJ28614118 (from Johnson & Johnson), or SSR 101010 (from Sanofi-Aventis)

**Nitric Oxide Modulatory Agents**

[0289] In certain embodiments, one or more nitric oxide modulatory agents are useful in combination with a first neurogenic agent of the present invention. One non-limiting example of a nitric oxide modulatory agent as known to the skilled person and useful herein includes sildenafil (Viagra®).

**Prolactin Agents**

[0290] In certain embodiments, one or more prolactin modulatory agents are useful in combination with a first neurogenic agent of the present invention.
Anti-viral Agents

[0291] In certain embodiments, one or more anti-viral agents are useful in combination with a first neurogenic agent of the present invention. Non-limiting examples of anti-viral agents as known to the skilled person and useful herein include ribavirin and amantadine as non-limiting examples.

Natural Product Agents

[0292] In certain embodiments, one or more natural agents, or a derivative thereof, are useful in combination with a first neurogenic agent of the present invention. Non-limiting examples of natural agents, or derivatives thereof, as known to the skilled person and useful herein include the following.

[0293] In some embodiments, the component or derivative thereof is in an isolated form, such as that which is separated from one or more molecules or macromolecules normally found with the component or derivative before use in a combination or method as disclosed herein. In other embodiments, the component or derivative is completely or partially purified from one or more molecules or macromolecules normally found with the component or derivative. Exemplary cases of molecules or macromolecules found with a component or derivative as described herein include a plant or plant part, an animal or animal part, and a food or beverage product.

[0294] Non-limiting examples such a component include folic acid, folate, methylfolate; a flavinoid, such as citrus flavonoid; a flavonol, such as Quercetin, Kaempferol, Myricetin, or Isorhamnetin; a flavone, such as Luteolin or Apigenin; a flavanone, such as Hesperetin, Naringenin, or Eriodictyol; a flavan-3-ol (including a monomeric, dimeric, or polymeric flavanol), such as (+)-Catechin, (+)-Gallocatechin, (-)-Epicatechin, (-)-Epigallocatechin, (-)-Epicatechin 3-gallate, (-)-Epigallocatechin 3-gallate, Theaflavin, Theaflavin 3-gallate, Theaflavin 3’,gallate, Theaflavin 3,3’ digallate, a Thearubigin, or Proanthocyanidin; an anthocyanidin, such as Cyanidin, Delphinidin, Malvidin, Pelargonidin, Peonidin, or Petunidin; an isoflavone, such as daidzein, genistein, or glycitein; flavopiridol; a prenylated chalcone, such as Xanthohumol; a prenylated flavanone, such as Isoxanthohumol; a non-prenylated chalcone, such as Chalconaringenin; a non-prenylated flavanone, such as Naringenin; Resveratrol; or an anti-oxidant neutraceutical (such as any present in chocolate, like dark chocolate or unprocessed or unrefined chocolate).
Additional non-limiting examples include a component of Gingko biloba, such as a flavo glycoside or a terpene. In some embodiments, the component is a flavanoid, such as a flavonol or flavone glycoside, or a quercetin or kaempferol glycoside, or rutin; or a terpenoid, such as ginkgolides A, B, C, or M, or bilobalide.

Further non-limiting examples include a component that is a flavanol, or a related oligomer, or a polyphenol as described in US2005/245601 AA, US2002/018807 AA, US2003/180406 AA, US2002/086833 AA, US2004/0236123, WO9809533, or WO9945788; a procyanidin or derivative thereof or polyphenol as described in US2005/171029 AA; a procyanidin, optionally in combination with L-arginine as described in US2003/104075 AA; a low fat cocoa extract as described in US2005/031762 AA; lipophilic bioactive compound containing composition as described in US2002/107292 AA; a cocoa extract, such as those containing one or more polyphenols or procyanidins as described in US2002/004523 AA; an extract of oxidized tea leaves as described in US Pat. 5,139,802 or 5,130,154; a food supplement as described in WO 2002/024002.

Calcitonin Receptor Agonist Agents and Parathyroid Hormone Agents

In certain embodiments, one or more calcitonin receptor agonist agents are useful in combination with a first neurogenic agent of the present invention. Non-limiting examples of such agents as known to the skilled person and useful herein include calcitonin or the Orphan peptide' PHM-27 (see Ma et al. "Discovery of novel peptide/receptor interactions: identification of PHM-27 as a potent agonist of the human calcitonin receptor." Biochem Pharmacol 2004 67(7): 1279-84). A further non-limiting example is the agonist from Kemia, Inc.

In certain alternative embodiments, the present agent may be a reported modulator of parathyroid hormone activity, such as parathyroid hormone, or a modulator of the parathyroid hormone receptor.

Antioxidant Agents

In certain embodiments, one or more antioxidant agents are useful in combination with a first neurogenic agent of the present invention. Non-limiting examples of antioxidant agents as known to the skilled person and useful herein include the following.
Non-limiting examples include N-acetylcysteine or acetylcysteine; disufenton sodium (or CAS RN 168021-79-2 or Cerovive); activin (CAS RN 104625-48-1); selenium; L-methionine; an alpha, gamma, beta, or delta, or mixed, tocopherol; alpha lipoic acid; Coenzyme Q; Benzimidazole; benzoic acid; dipyridamole; glucosamine; IRFI-0.16 (2(2,3-dihydro-5-acetoxy-4,6,7-trimethylbenzofuranyl) acetic acid); L-carnosine; L-Histidine; glycine; flavocoxid (or LIMBREL); baicalin, optionally with catechin (3,3’,4’, 5,7-pentahydroxyflavan (2R,3S form)), and/or its stereo-isomer; masoprocol (CAS RN 27686-84-6); mesna (CAS RN 19767-45-4); probucol (CAS RN 23288-49-5); silibinin (CAS RN 22888-70-6); sorbinil (CAS RN 68367-52-2); spermine; tangeretin (CAS RN 481-53-8); butylated hydroxyanisole (BHA); butylated hydroxytoluene (BHT); propyl gallate (PG); tertiary-butyl-hydroquinone (TBHQ); nordihydroguaiaretic acid (CAS RN 500-38-9); astaxanthin (CAS RN 472-61-7); or an antioxidant flavonoid.

Additional non-limiting examples include a vitamin, such as vitamin A (Retinol) or C (Ascorbic acid) or E (including Tocotrienol and/or Tocopherol); a vitamin cofactors or mineral, such as Coenzyme QIO (CoQIO), Manganese, or Melatonin; a carotenoid terpenoid, such as Lycopene, Lutein, Alpha-carotene, Beta-carotene, Zeaxanthin, Astaxanthin, or Canthaxanthin; a non-carotenoid terpenoid, such as Eugenol; a flavonoid polyphenols (or bioflavonoid); a flavonol, such as Resveratrol, Pterostilbene (methoxylated analogue of resveratrol), Kaempferol, Myricetin, Isorhamnetin, a Proanthocyanidin, or a tannin; a flavone, such as Quercetin, rutin, Luteolin, Apigenin, or Tangerin; a flavanone, such as Hesperetin or its metabolite hesperidin, naringenin or its precursor naringin, or Eriodictyol; a flavan-3-ols (anthocyanidins), such as Catechin, Gallocatechin, Epicatechin or a gallate form thereof, Epigallocatechin or a gallate form thereof, Theaflavin or a gallate form thereof, or a Thearubigin; an isoflavone phytoestrogens, such as Genistein, Daidzein, or Glycitein; an anthocyanins, such as Cyanidin, Delphinidin, Malvidin, Pelargonidin, Peonidin, or Petunidin; a phenolic acid or ester thereof, such as Ellagic acid, Gallic acid, Salicylic acid, Rosmarinic acid, Cinnamic acid or a derivative thereof like ferulic acid, Chlorogenic acid, Chicoric acid, a Gallotannin, or an Ellagitannin; a nonflavonoid phenolic, such as Curcumin; an anthoxanthin, betacyanin, Citric acid, Uric acid, R-α-lipoic acid, or Silymarin.

Further non-limiting examples include l-(carboxymethylthio)tetradecane; 2,2,5,7,8-pentamethyl- 1-hydroxychroman; 2,2,6,6-tetramethyl-4-piperidinol-N-oxyl; 2,5-di-tert-butylhydroquinone; 2-tert-butylhydroquinone; 3,4-dihydroxyphenylethanol; 3-hydroxypyridine; 3-hydroxytamoxifen; 4-coumaric acid; 4-hydroxyanisole; 4-
hydroxyphenylethanol; 4-methylcatechol; 5,6,7,8-tetrahydrobiopterin; 6,6'-methylenebis(2,2-dimethyl-4-methanesulfonic acid-1,2-dihydroquinoline); 6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid; 6-methyl-2-ethyl-3-hydroxyipyridine; 6-0-palmitoylascorbic acid; acetovanillone; acteoside; Actovegin; allicin; allyl sulfide; alphapentyl-3-(2-quinolinylmethoxy)benzenemethanol; alpha-tocopherol acetate; apolipoprotein A-IV; bemethyl; boldine; bucillamine; Calcium Citrate; Canthaxanthin; crocetin; diallyl trisulfide; dicarbine; dihydrolipoic acid; dimephosphon; ebselen; Efamol; enkephalin-Leu, Ala(2)-Arg(6); Ergothioneine; esculetin; essential 303 forte; Ethenonium; etofyllinclofibrate; fenozan; glaucine; H290-51; histidyl-proline diketopiperazine; hydroquinone; hypotaurine; idebenone; indole-3-carbinol; isoascorbic acid; kojic acid, lacidipine, lodoxamide tromethamine; mexidol; morin; N,N'-diphenyl-4-phenylenediamine; N-isopropyl-N-phenyl-4-phenylenediamine; N-monoacetylcystine; nicaraven, nicotinoyl-GABA; nitecapone; nitroxy1; nobiletin; oxymethacil; p-tert-butyl catechol; phenidone; pramipexol; proanthocyanidin; procyanidin; prolinedithiocarbamate; Propyl Gallate; purpurogallin; pyrrolidine dithiocarbamic acid; rebamipide; retinol palmitate; salvin; Selenious Acid; sesamin; sesamol; sodium selenate; sodium thiosulfate; theaflavin; thiazolidine-4-carboxylic acid; tirilazad; tocopherylquinone; tocotrienol, alpha; a Tocotrienol; tricyclodecane-9-y1-xanthogenate; turmeric extract; U 74389F; U 74500A; U 785 17F; ubiquinone 9; vanillin; vinpocetine; xylometazoline; zeta Carotene; zilascorb; zinc thionein; or zonisamide.

Norepinephrine Receptor Modulator Agents

[0303] In certain embodiments, one or more norepinephrine receptor modulatory agents are useful in combination with a first neurogenic agent of the present invention. Non-limiting examples of such agents as known to the skilled person and useful herein include the following.

[0304] Non-limiting examples include Atomoxetine (Strattera); a norepinephrine reuptake inhibitor, such as talsupram, tomoxetine, nortriptiyline, nisoxetine, reboxetine (described, e.g., in U.S. Pat. 4,229,449), or tomoxetine (described, e.g., in U.S. Pat. 4,314,081); or a direct agonist, such as a beta adrenergic agonist.
Adrenergic Receptor Modulator Agents

In certain embodiments, one or more adrenergic receptor modulatory agents are useful in combination with a first neurogenic agent of the present invention. Non-limiting examples of such agents as known to the skilled person and useful herein include the following.

Non-limiting examples include an alpha adrenergic agonist such as etilefrine or a reported agonist of the α2-adrenergic receptor (or α2 adrenoceptor) like clonidine (CAS RN 4205-90-7), yohimbine, mirtazepine, atipamezole, carvedilol; dexmedetomidine or dexmedetomidine hydrochloride; ephedrine, epinephrine; etilefrine; lidamidine; tetramethylpyrazine; tizanidine or tizanidine hydrochloride; apraclonidine; bitolterol mesylate; brimonidine or brimonidine tartrate; dipivefrin (which is converted to epinephrine in vivo); guanabenz; guanfacine; methyldopa; alphamethylnoradrenaline; mivazerol; natural ephedrine or D(-)ephedrine; any one or any mixture of two, three, or four of the optically active forms of ephedrine; CHF1035 or nolomirole hydrochloride (CAS RN 138531-51-8); or lofexidine (CAS RN 31036-80-3).

Alternative non-limiting examples include an adrenergic antagonist such as a reported antagonist of the α2-adrenergic receptor like yohimbine (CAS RN 146-48-5) or yohimbine hydrochloride, idazoxan, fluparoxan, mirtazepine, atipamezole, or RX781094 (see Elliott et al. "Peripheral pre and postjunctional alpha 2-adrenoceptors in man: studies with RX78 1094, a selective alpha 2 antagonist." J Hypertens Suppl. 1983 1(2): 109-11).

Other non-limiting embodiments include a reported modulator of an α1-adrenergic receptor such as cirazoline; modafinil; ergotamine; metaraminol; methoxamine; midodrine (a prodrug which is metabolized to the major metabolite desglymidodrine formed by deglycination of midodrine); oxymetazoline; phenylephrine; phenylpropanolamine; or pseudoephedrine.

Further non-limiting embodiments include a reported modulator of a beta adrenergic receptor such as arbutamine, befunolol, cimaterol, higenamine, isoxsuprine, methoxyphenamine, oxyfedrine, ractopamine, tretquinol, or TQ-1016 (from TheraQuest Biosciences, LLC), or a reported β1-adrenergic receptor modulator such as prenalterol, Ro 363, or xamoterol or a reported β1-adrenergic receptor agonist like dobutamine.

Alternatively, the reported modulator may be of a β2-adrenergic receptor such as levosalbutamol (CAS RN 34391-04-3), metaproterenol, MN-221 or KUR-1246 ((-)-bis(2-
{(2S)-2-(((2R)-2-hydroxy-2-[4-hydroxy-3-(2-hydroxyethyl)phenyl]ethyl)amino)-1,2,3,4-tetrahydronaphthalen-7-yl)oxy}-N,N-dimethylacetamide monosulfate or bis(2-(((2S)-2-((2R)-2-hydroxy-2-[4-hydroxy-3-(2-hydroxyethyl)phenyl]ethyl)amino)-1,2,3,4-tetrahydronaphthalen-7-yl)oxy]-N,N-dimethylacetamide) sulfate or CAS RN 194785-31-4), nylidrin, orciprenaline, pirbuterol, procaterol, reproterol, ritodrine, salmeterol, salmeterol xinafoate, terbutaline, tulobuterol, zinterol or bromoacetylalprenololmthane, or a reported \( \beta \)-adrenergic receptor agonist like albuterol, albuterol sulfate, salbutamol (CAS RN 35763-26-9), clenbuterol, broxaterol, dopexamine, formoterol, formoterol fumarate, isoetharine, levalbuterol tartrate hydrofluoroalkane, or mabuterol.

[0311] Additional non-limiting embodiments include a reported modulator of a \( \beta_3 \)-adrenergic receptor such as AJ-9677 or TAK677 ([3-((2R)-((2R)-(3-chlorophenyl)-2-hydroxyethyl)amino)propyl]-lH-indol-7-yloxy]acetic acid), or a reported \( \beta_3 \)-adrenergic receptor agonist like SR5861 IA (described in Simiand et al., Eur J Pharmacol, 219:193—201 (1992), BRL 26830A, BRL 35135, BRL 37344, CL 316243 or ICI D71 14.

[0312] Further alternative embodiments include a reported nonselective alpha and beta adrenergic receptor agonist such as epinephrine or ephedrine; a reported nonselective alpha and beta adrenergic receptor antagonist such as carvedilol; a \( \beta_1 \) and \( \beta_2 \) adrenergic receptor agonist such as isoproteotenol; or a \( \beta_1 \) and \( \beta_2 \) adrenergic receptor antagonist such as CGP 12177, fenoterol, or hexoprenaline.

[0313] Non-limiting examples of reported adrenergic agonists include albuterol, albuterol sulfate, salbutamol (CAS RN 35763-26-9), clenbuterol, adrafinil, and SR5861 IA (described in Simiand et al., Eur J Pharmacol, 219:193-201 (1992)), clonidine (CAS RN 4205-90-7), yohimbine (CAS RN 146-48-5) or yohimbine hydrochloride, arbutamine; befunolol; BRL 26830A; BRL 35135; BRL 37344; bromoacetylalprenololmthane; broxaterol; carvedilol; CGP 12177; cimaterol; cirazoline; CL 316243; Clenbuterol; denopamine; dexametomidine or dexametomidine hydrochloride; Dobutamine, dopexamine, Ephedrine, Epinephrine, Etilefrine; Fenoterol; formoterol; formoterol fumarate; Hexoprenaline; higenamine; ICI D71 14; Isoetharine; Isoproterenol; Isoxsuprine; levalbuterol tartrate hydrofluoroalkane; lidamidine; mabuterol; methoxyphenamine: modafinil; Nylidrin; Orciprenaline; Oxyfedrine; pirbuterol; Prenalterol; Procaterol; ractopamine; reproterol; Ritodrine; Ro 363; salmeterol; salmeterol xinafoate; Terbutaline; tetramethylpyrazine; tizanidine or tizanidine hydrochloride; Tretoquinol; tulobuterol; Xamoterol; or zinterol. Additional non-limiting
examples include Apraclonidine, Bitolterol Mesylate, Brimonidine or Brimonidine tartrate, Dipivefrin (which is converted to epinephrine in vivo), Epinephrine, Ergotamine, Guanabenz, guanfacine, Metaproterenol, Metaraminol, Methoxamine, Metyldopa, Midodrine (a prodrug which is metabolized to the major metabolite desglymidodrine formed by deglycination of midodrine), Oxymetazoline, Phenylephrine, Phenylpropanolamine, Pseudoephedrine, alphamethylnoradrenaline, mivazerol, natural ephedrine or D(-)ephedrine, any one or any mixture of two, three, or four of the optically active forms of ephedrine, CHF1035 or nolomirole hydrochloride (CAS RN 138531-51-8), AJ-9677 or TAK677 ([3-[(2R)-[[(2R)-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]-IH-indol-7-yl]oxy) acetic acid), MN-221 or KUR-1246 ((-)bis-[(2S)-2-[(2R)-2-hydroxy-2-[4-hydroxy-3-(2-hydroxyethyl)phenyl]ethyl]amino]-1,2,3,4-tetrahydronaphthalen-7-yl]oxy-N,N-dimethylacetamide)monosulfate or bis-[(2S)-2-[(2R)-2-hydroxy-2-[4-hydroxy-3-(2-hydroxyethyl)phenyl]ethyl]amino]-1,2,3,4-tetrahydronaphthalen-7-yl]oxy-N,N-dimethylacetamide sulfate or CAS RN 194785-31-4), levosalbutamol (CAS RN 34391-04-3), lofexidine (CAS RN 31036-80-3) or TQ-1016 (from TheraQuest Biosciences, LLC).

[0314] In certain further embodiments, a reported adrenergic antagonist, such as idazoxan or fluparoxan, may be used as an agent in a combination described herein.

**Carbonic Anhydrase Agents**

[0315] In certain embodiments, one or more carbonic anhydrase modulatory agents are useful in combination with a first neurogenic agent of the present invention. Non-limiting examples of such agents as known to the skilled person and useful herein include the following.

[0316] Non-limiting examples of such an agent include acetazolamide, benzenesulfonamide, benzolamide, brinzolamide, dichlophenamide, dorzolamide or dorzolamide HCl, ethoxzolamide, flurbiprofen, mafenide, methazolamide, sezolamide, zonisamide, bendroflumethiazide, benzthiazide, chlorothiazide, cyclothiazide, dansylamide, diazoxide, ethinamate, furosemide, hydrochlorothiazide, hydroflumethiazide, mercuribenzoic acid, methyclothiazide, trichlormethiazide, amlodipine, cyanamide, or a benzenesulfonamide. Additional non-limiting examples of such an agent include (4s-Trans)-4-(Ethylamino)-5,6-Dihydro-6-Methyl-4h-Thieno(2,3-B)Thiopyran-2-Sulfonamide-7,7-Dioxide; (4s-Trans)-4-(Methylamino)-5,6-Dihydro-6-Methyl-4h-Thieno(2,3-B)Thiopyran-2-
Sulfonamide-7,7-Dioxide; (R)-N-(3-Indol-1-Yl-2-Methyl-Propyl)-4-Sulfamoyl-Benzamide; 
(S)-N-(3-Indol-1-Yl-2-Methyl-Propyl)-4-Sulfamoyl-Benzamide; 1,2,4-Triazole; 1-Methyl-3-Oxo-1,3-Dihydro-Benzo[C]Isothiazole-5-Sulfonic Acid Amide; 2,6-Difluorobenzenesulfonamide; 3,5-Difluorobenzenesulfonamide; 3-Mercure-4-Aminobenzenesulfonamide; 3-Nitro-4-(2-Oxo-Pyrroloidin-1-Yl)-Benzenesulfonamide; 4-(Aminosulfonfyl)-N-[(2,3,4-Trifluorophenyl)Methyl]-Benzamide; 4-(Aminosulfonfyl)-N-[(2,4,6-Trifluorophenyl)Methyl]-Benzamide; 4-(Aminosulfonfyl)-N-[(2,4-Difluorophenyl)Methyl]-Benzamide; 4-(Aminosulfonfyl)-N-[(2,5-Difluorophenyl)Methyl]-Benzamide; 4-(Aminosulfonfyl)-N-[(3,4,5-Trifluorophenyl)Methyl]-Benzamide; 4-(Aminosulfonfyl)-N-[(4-Fluorophenyl)Methyl]-Benzamide; 4-(Hydroxymercury)Benzoic Acid; 4-Fluorobenzenesulfonamide; 4-Methylimidazole; 4-Sulfonamide-[1-(4-Aminobutane)]Benzamide; 4-Sulfonamide-[(4-(Thiomethylaminobutane)]Benzamide; 5-Acetamido-1,3,4-Thiadiazole-2-Sulfonamide; 6-Oxo-8,9,10,1-Tetrahydro-7h-Cyclohepta[C][1]Benzopyran-3-O-Sulfamate; (4-sulfamoyl-phenyl)-thiocarbamic acid O-(2-thiophen-3-yl-ethyl) ester; (R)-4-ethylamino-3,4-dihydro-2-(2-methylethyl)-2H-thieno[3,2-E]-1,2-thiazine-6-sulfonamide 1,1-dioxide; 3,4-dihydro-4-hydroxy-2-(2-thienymethyl)-2H-thieno[3,2-E]-1,2-thiazine-6-sulfonamide-1,1-dioxide; 3,4-dihydro-4-hydroxy-2-(4-methoxyphenyl)-2H-thieno[3,2-E]-1,2-thiazine-6-sulfonamide-1,1-dioxide; N-[(4-methoxyphenyl)methyl][2,5-thiophenedesulfonamide; 2-(3-methoxyphenyl)-2H-thieno[3,2-E]-1,2-thiazine-6-sulfinamide-1,1-dioxide; (R)-3,4-dihydro-2-(3-methoxyphenyl)-4-methylamino-2H-thieno[3,2-E]-1,2-thiazine-6-sulfonamide-1,1-dioxide; (S)-3,4-dihydro-2-(3-methoxyphenyl)-4-methylamino-2H-thieno[3,2-E]-1,2-thiazine-6-sulfonamide-1,1-dioxide; 3,4-dihydro-2-(3-methoxyphenyl)-2H-thieno[3,2-E]-1,2-thiazine-6-sulfonamide-1,1-dioxide; [2h-Thieno[3,2-E]-1,2-Thiazine-6-Sulfonamide,2-(3-Hydroxyphenyl)-3-(4-MoΦ holinyl)-, 1,1-Dioxygen; [2h-Thieno[3,2-E]-1,2-Thiazine-6-Sulfonamide,2-(3-Methoxyphenyl)-3-(4-Morpholinyl)-, 1,1-Dioxygen; Aminodi(Ethylxoy)Ethylaminocarbonylbenzenesulfonamide; N-(2,3,4,5,6-Pentaflouro-Benzyl)-4-Sulfamoyl-Benzamide; N-(2,6-Difluoro-Benzyl)-4-Sulfamoyl-Benzamide; N-(2-Flouro-Benzyl)-4-Sulfamoyl-Benzamide; N-(2-Thieryl methyl)-2,5-Thiophenedisulfonamide; N-[2-(IH-Indol-5-Yl)-Butyl]-4-Sulfamoyl-Benzamide; N-Benzyl-4-Sulfamoyl-Benzamide; or Sulfamic Acid 2,3-O-(1-Methylethylidene)-4,5-O-Sulfonyl-Beta-Fructopyranose Ester.
Catechol-O-Methyltransferase (COMT) Agents

In certain embodiments, one or more COMT agents are useful in combination with a first neurogenic agent of the present invention. Non-limiting examples of COMT agents as known to the skilled person and useful herein include floproprion, or a COMT inhibitor, such as tolcapone (CAS RN 134308-13-7), nitecapone (CAS RN 116313-94-1), or entacapone (CAS RN 116314-67-1 or 130929-57-6).

Hedgehog Agents

In certain embodiments, one or more agents that are a modulator of hedgehog pathway or signaling activity are useful in combination with a first neurogenic agent of the present invention. Non-limiting examples of such agents as known to the skilled person and useful herein include cyclopamine, jervine, ezetimibe, regadenoson (CAS RN 313348-27-5, or CVT-3146), any hedgehog modulatory compound described in U.S. Pat. 6,683,192 or identified as described in U.S. Pat. 7,060,450, or CUR-61414 or any hedgehog modulatory compound described in U.S. Pat. 6,552,016.

IMPDH Agents

In certain embodiments, one or more Inosine monophosphate dehydrogenase (IMPDH) modulatory agents are useful in combination with a first neurogenic agent of the present invention. Non-limiting examples of such agents as known to the skilled person and useful herein include mycophenolic acid or mycophenolate mofetil (CAS RN 128794-94-5).

Sigma Receptor Agents

In certain embodiments, one or more agents that modulates a sigma receptor are useful in combination with a first neurogenic agent of the present invention. Non-limiting examples of such agents as known to the skilled person and useful herein include the following.

The sigma receptor may include sigma-1 and sigma-2. Non-limiting examples of such a modulator include an agonist of sigma-1 and/or sigma-2 receptor, such as (+)-pentazocine, SKF 10,047 (N-allylnormetazocine), or 1,3-di-o-tolylguanidine (DTG). Additional non-limiting examples include SPD-473 (from Shire Pharmaceuticals); a molecule with sigma modulatory activity as known in the field (see e.g., Bowen et al., Pharmaceutica...
Acta Helvetiae 74: 211-218 (2000); a guanidine derivative such as those described in U.S. Pat. Nos. 5,489,709; 6,147,063; 5,298,657; 6,087,346; 5,574,070; 5,502,255; 4,709,094; 5,478,863; 5,385,946; 5,312,840; or 5,093,525; WO9014067; an antipsychotic with activity at one or more sigma receptors, such as haloperidol, rimcazole, perphenazine, fluphenazine, (-)-butaclamol, acetophenazine, trifluoperazine, molindone, pimozide, thioridazine, chlorpromazine and triflupromazine, BMY 14802, BMY 13980, remoxipride, tiospirone, cinuperone (HR 375), or WY47384.


[0323] Further non-limiting examples include a sigma-1 agonist, such as IPAG (1-(4-iodophenyl)-3-(2-adamantyl)guanidine); pre-084; carbetapentane; 4-IBP; L-687,384 and related compounds described in Middlemiss et al., Br. J. Pharm., 102: 153 (1991); BD 737 and related compounds described in Bowen et al., J Pharmacol Exp Ther., 262(1): 32-40 (1992)); OPC-14523 or a related compound described in Oshiro et al., J Med Chem., 43(2): 177-89 (2000); a sigma-1 selective agonist, such as igmesine; (+)-benzomorphans, such as (-)-pentazocine and (+)-ethylketocyclazocine; SA-4503 or a related compound described in U.S. Pat. No. 5,736,546 or by Matsuno et al., Eur J Pharmacol., 306(1-3): 271-9 (1996); SK&F 10047; or ifenprodil; a sigma-2 agonist, such as haloperidol, (+)-5,8-disubstituted morphan-7-ones, including CB 64D, CB 184, or a related compound described in Bowen et

[0324] Alternative non-limiting examples include a sigma-1 antagonist such as BD-1047 (N(-)[2-(3,4-dichlorophenyl)ethyl]-N-methyl-2-(dimethylamino)ethylamine), BD-1063 (1-[(2-(3,4-dichlorophenyl)ethyl)-4-methylpiperazine, rimcazole, haloperidol, BD-1047, BD-1063, BMY 14802, DuP 734, NE-100, AC915, or R-(-)-3-PPP. Particular non-limiting examples include fluoxetine, fluvoxamine, citalopram, sertraline, clorgyline, imipramine, igmesine, opipramol, siramesine, SL 82.0715, imcazole, DuP 734, BMY 14802, SA 4503, OPC 14523, panamasine, or PRX-00023.

[0325] Other non-limiting examples of an agent in combination with a first neurogenic agent include acamprosate (CAS RN 77337-76-9); a growth factor, like LIF, EGF, FGF, bFGF or VEGF as non-limiting examples; octreotide (CAS RN 83150-76-9); an NMDA modulator like DTG, (+)-pentazocine, DHEA, Lu 28-179 (1'-[4-[[1-(4-fluorophenyl)]-IH-indol-3-yl]-1-butyl]-spiro[isobenzofuran-1(3H), 4'piperidine]), BD 1008 (CAS RN 138356-08-8), ACEA1021 (Licostinel or CAS RN 153504-81-5), GV150526A (Gavestinel or CAS RN 153436-22-7), sertraline, clorgyline, or memantine as non-limiting examples; or metformin.

[0326] Of course a further combination therapy may also be that of a first neurogenic agent in combination with one or more other neurogenic agents being a non-chemical based therapy. Non-limiting examples include the use of psychotherapy for the treatment of many conditions described herein, such as the psychiatric conditions, as well as behavior modification therapy such as that use in connection with psychological therapy or a weight loss program. Another non-limiting example comprises exercise and an exercise program.
Kits Comprising Compositions of the Present Invention

[0327] In certain embodiments, the invention provides kits (compositions of matter) comprising one or more HMGCR modulating agents, optionally in combination with a second neurogenic agent, wherein the neurogenic agent or agents are packaged together with instructions for using the composition or compositions in the kit in a method of the present invention. In certain embodiments, that comprise a combination of neurogenic agents, each agent is contained in a separate vial within the packaging of the kit. In certain embodiments, that comprise a combination of neurogenic agents, the combination of agents is contained within a single vial so as to be in a single formulation, optionally in a single unit dose. In certain embodiments the kit further comprises a pharmaceutically acceptable carrier which is either packaged in a separate vial or contained with one or more neurogenic agents in a vial.

Methods of Using Compositions

[0328] Certain embodiments herein provide methods of using a neurogenic agent or combinations of neurogenic agents. Non-limiting examples include methods of treating a nervous system disorder and a method of increasing neurodifferentiation of a cell or tissue. One or more of the compositions provided herein comprising an HMGCR modulating agent, or combinations therewith can be used in any of the methods of the invention. Applicants reserve the right to explicitly disclaim one or more specific second agents disclosed above from a given method in the specification or the claims. Applicants also reserve the right to explicitly disclaim one or more specific treatments disclosed herein for use with a given agent or combination of agents.

Treating a Nervous System Disorder

[0329] Methods described herein can be used to treat any disease or condition for which it is beneficial to promote or otherwise stimulate or increase neurogenesis, for example. Thus, certain embodiments of the methods described herein are to achieve a therapeutic result by increasing neurogenesis. Certain methods described herein can be used to treat any disease or condition susceptible to treatment by increasing neurogenesis.

[0330] In some embodiments, a disclosed method is applied to modulating neurogenesis in vivo, in vitro, or ex vivo. For in vivo embodiments, the cells may be present in a tissue or organ of a subject animal or human being. Non-limiting examples of cells include those
capable of neurogenesis, such as to result, whether by differentiation or by a combination of
differentiation and proliferation, in differentiated neural cells. As described herein,
neurogenesis includes the differentiation of neural cells along different potential lineages. In
some embodiments, the differentiation of neural stem or progenitor cells is along a neuronal
cell lineage to produce neurons. In other embodiments, the differentiation is along both
neuronal and glial cell lineages. In additional embodiments, the disclosure further includes
differentiation along a neuronal cell lineage to the exclusion of one or more cell types in a
glial cell lineage. Non-limiting examples of glial cell types include oligodendrocytes and
radial glial cells, as well as astrocytes, which have been reported as being of an "astroglial
lineage". Therefore, certain embodiments of the disclosure include differentiation along a
neuronal cell lineage to the exclusion of one or more cell types selected from
oligodendrocytes, radial glial cells, and astrocytes.

[0331] In other embodiments, the disease or condition being treated is associated with pain
and/or addiction, but in contrast to known methods, the disclosed treatments are substantially
mediated by increasing neurogenesis. For example, in some embodiments, methods described
herein involve increasing neurogenesis ex vivo, such that a composition containing neural
stem cells, neural progenitor cells, and/or differentiated neural cells can subsequently be
administered to an individual to treat a disease or condition. In some embodiments, methods
described herein allow treatment of diseases characterized by pain, addiction, and/or
depression to be treated by directly replenishing, replacing, and/or supplementing neurons
and/or glial cells. In further embodiments, methods described herein enhance the growth
and/or survival of existing neural cells, and/or slow or reverse the loss of such cells in a
neurodegenerative condition.

[0332] Examples of diseases and conditions treatable by the methods described herein
include, but are not limited to, neurodegenerative disorders and neural disease, such as
dementias (e.g., senile dementia, memory disturbances/memory loss, dementias caused by
neurodegenerative disorders (e.g., Alzheimer's, Parkinson's disease, Parkinson's disorders,
Huntington's disease (Huntington's Chorea), Lou Gehrig's disease, multiple sclerosis, Pick's
disease, Parkinsonism dementia syndrome), progressive subcortical gliosis, progressive
supranuclear palsy, thalamic degeneration syndrome, hereditary aphasia, amyotrophic lateral
sclerosis, Shy-Drager syndrome, and Lewy body disease; vascular conditions (e.g., infarcts,
hemorrhage, cardiac disorders); mixed vascular and Alzheimer's; bacterial meningitis;
Creutzfeld-Jacob Disease; and Cushing's disease.
The disclosed embodiments also provide for the treatment of a nervous system disorder related to neural damage, cellular degeneration, a psychiatric condition, cellular (neurological) trauma and/or injury (e.g., subdural hematoma or traumatic brain injury), toxic chemicals (e.g., heavy metals, alcohol, some medications), CNS hypoxia, or other neurologically related conditions. In practice, the disclosed compositions and methods may be applied to a subject or patient afflicted with, or diagnosed with, one or more central or peripheral nervous system disorders in any combination. Diagnosis may be performed by a skilled person in the applicable fields using known and routine methodologies which identify and/or distinguish these nervous system disorders from other conditions.

Non-limiting examples of nervous system disorders related to cellular degeneration include neurodegenerative disorders, neural stem cell disorders, neural progenitor cell disorders, degenerative diseases of the retina, and ischemic disorders. In some embodiments, an ischemic disorder comprises an insufficiency, or lack, of oxygen or angiogenesis, and non-limiting example include spinal ischemia, ischemic stroke, cerebral infarction, multi-infarct dementia. While these conditions may be present individually in a subject or patient, the disclosed methods also provide for the treatment of a subject or patient afflicted with, or diagnosed with, more than one of these conditions in any combination.

In additional embodiments, the disclosure includes a method of stimulating or increasing neurogenesis in a subject or patient with stimulation of angiogenesis in the subject or patient. The co-stimulation may be used to provide the differentiating and/or proliferating cells with increased access to the circulatory system. The neurogenesis is produced by the first neurogenic agent, optionally in combination with one or more other neurogenic agents, as described herein. An increase in angiogenesis may be mediated by a methods known to the skilled person, including administration of a angiogenic factor or treatment with an angiogenic therapy. Non-limiting examples of angiogenic factors or conditions include vascular endothelial growth factor (VEGF), angiopoietin-1 or -2, erythropoietin, exercise, or any combination thereof.

So in some embodiments, the disclosure includes a method comprising administering i) a first neurogenic agent, optionally in combination with one or more other neurogenic agents, and ii) one or more angiogenic factors to a subject or patient. In other embodiments, the disclosure includes a method comprising administering i) a first neurogenic agent, optionally in combination with one or more other neurogenic agents, to a subject or
patient with ii) treating said subject or patient with one or more angiogenic conditions. The subject or patient may be any as described herein.

[0337] The co-treatment of a subject or patient includes simultaneous treatment or sequential treatment as non-limiting examples. In cases of sequential treatment, the administration of a first neurogenic agent of the present invention, optionally with one or more other neurogenic agents, may be before or after the administration of an angiogenic factor or condition.

[0338] Non-limiting embodiments of nervous system disorders related to a psychiatric condition include neuropsychiatric disorders and affective disorders. As used herein, an affective disorder refers to a disorder of mood such as, but not limited to, depression, major depression, treatment refractory depression, post-traumatic stress disorder (PTSD), hypomania, panic attacks, excessive elation, bipolar depression, bipolar disorder (manic-depression), and seasonal mood (or affective) disorder. Other non-limiting embodiments include schizophrenia and other psychoses, lissencephaly syndrome, anxiety syndromes, anxiety disorders, phobias, stress and related syndromes (e.g., panic disorder, phobias, adjustment disorders, migraines), cognitive function disorders, aggression, drug and alcohol abuse, drug addiction, and drug-induced neurological damage, obsessive compulsive behavior syndromes, borderline personality disorder, non-senile dementia, post-pain depression, post-partum depression, and cerebral palsy.

[0339] Accordingly, certain embodiments herein provide a method of treating a nervous system disorder in a mammalian subject in need thereof, said method comprising administering to the subject a neurogenic amount of a composition, comprising: a first neurogenic agent of the present invention; and a second neurogenic agent, wherein the first and second agents are in combination in a single formulation.

[0340] In certain preferred embodiments, the second neurogenic agent comprises an antidepressant, an antipsychotic, or a combination of an antidepressant and an antipsychotic.

[0341] In certain embodiments, the nervous system disorder is related to a nerve cell trauma, a psychiatric condition, or a neurologically related condition, or any combination thereof.
In certain embodiments, the nervous system disorder is selected from the group consisting of: a neural stem cell disorder, a neural progenitor cell disorder, a degenerative disease of the retina, an ischemic disorder, and any combination thereof.

In certain embodiments, the psychiatric condition is selected from the group consisting of: an affective disorder, depression, post-traumatic stress disorder (PTSD), hypomania, panic attacks, anxiety, excessive elation, bipolar depression, bipolar disorder, seasonal mood disorder, schizophrenia, psychosis, lissencephaly syndrome, an anxiety syndrome, an anxiety disorder, a phobia, stress, a stress syndrome, a cognitive function disorder, aggression, drug abuse, alcohol abuse, an obsessive compulsive behavior syndrome, a borderline personality disorder, non-senile dementia, post-pain depression, post-partum depression, cerebral palsy, and any combination thereof.

In certain embodiments, the psychiatric condition is selected from the group consisting of: depression, anxiety, bipolar disorder, schizophrenia, and any combination thereof.

In certain embodiments, the psychiatric condition is depression and/or PTSD.

In certain embodiments, the nerve cell trauma is selected from the group consisting of: an injury and a surgery, or a combination thereof.

In certain embodiments, the injury or the surgery is related to: retinal injury or surgery, cancer treatment, infection, inflammation, an environmental toxin, or any combination thereof.

In certain embodiments, the neurologically related condition is selected from the group consisting of: a learning disorder, autism, an attention deficit disorder, narcolepsy, a sleep disorder, a cognitive disorder, epilepsy, temporal lobe epilepsy, and any combination thereof.

In certain embodiments, the mammalian subject is a human patient.

Applicants reserve the right to explicitly exclude one or more specific disease indications or disorders from any given method of treatment in the specification or in the claims.

Some embodiments include a method of modulating a neurogenic response or increasing neurodifferentiation by contacting one or more neural cells with a first neurogenic
agent, optionally in combination with one or more other neurogenic agents. In some embodiments, the amount of a first neurogenic agent, or a combination thereof with one or more other neurogenic agents, may be selected to be effective to produce an improvement in a treated subject, or a detectable neurogenic response or increase neurodifferentiation in vitro, in vivo, or ex vivo. In some embodiments, the amount is one that also minimizes clinical side effects.

[0352] In some embodiments, and preferably if compared to a reduced level of cognitive function, a method of the invention may be for enhancing or improving cognitive function in a subject or patient. Thus, in some embodiments, the method may comprise administering a first neurogenic agent, optionally in combination with one or more other neurogenic agents, to a subject or patient to enhance or improve a condition comprising a decline or decrease of cognitive function. In some embodiments, the decline in cognitive function results from or is a symptom of a therapy and/or condition that is neurotoxic or inhibits neurogenesis. Certain embodiments provide methods for treatment to enhance or maintain the cognitive function of a subject or patient. In some embodiments, the maintenance or stabilization of cognitive function may be at a level, or thereabouts, present in a subject or patient in the absence of a therapy and/or condition that reduces cognitive function. In some alternative embodiments, the maintenance or stabilization may be at a level, or thereabouts, present in a subject or patient as a result of a therapy and/or condition that reduces cognitive function.

[0353] In some embodiments, these methods optionally include assessing or measuring cognitive function of the subject or patient before, during, and/or after administration of the treatment to detect or determine the effect thereof on cognitive function. So in one embodiment, a methods may comprise i) treating a subject or patient that has been previously assessed for cognitive function and ii) reassessing cognitive function in the subject or patient during or after the course of treatment with a composition of the present invention. The assessment may measure cognitive function for comparison to a control or standard value (or range) in subjects or patients in the absence of first neurogenic agent, or a combination thereof with one or more other neurogenic agents. This may be used to assess the efficacy of the first neurogenic agent, alone or in a combination, in alleviating the reduction in cognitive function.

[0354] Examples of nervous system disorders related to cellular or tissue trauma and/or injury include, but are not limited to, neurological traumas and injuries, surgery related
trauma and/or injury, retinal injury and trauma, injury related to epilepsy, cord injury, spinal cord injury, brain injury, brain surgery, trauma related brain injury, trauma related to spinal cord injury, brain injury related to cancer treatment, spinal cord injury related to cancer treatment, brain injury related to infection, brain injury related to inflammation, spinal cord injury related to infection, spinal cord injury related to inflammation, brain injury related to environmental toxin, and spinal cord injury related to environmental toxin.

[0355] Non-limiting examples of nervous system disorders related to other neurologically related conditions include learning disorders, memory disorders, age-associated memory impairment (AAMI) or age-related memory loss, autism, learning or attention deficit disorders (ADD or attention deficit hyperactivity disorder, ADHD), narcolepsy, sleep disorders and sleep deprivation (e.g., insomnia, chronic fatigue syndrome), cognitive disorders, epilepsy, injury related to epilepsy, and temporal lobe epilepsy.

[0356] Other non-limiting examples of diseases and conditions treatable by the methods described herein include, but are not limited to, hormonal changes (e.g., depression and other mood disorders associated with puberty, pregnancy, or aging (e.g., menopause)); and lack of exercise (e.g., depression or other mental disorders in elderly, paralyzed, or physically handicapped patients); infections (e.g., HIV); genetic abnormalities (down syndrome); metabolic abnormalities (e.g., vitamin B12 or folate deficiency); hydrocephalus; memory loss separate from dementia, including mild cognitive impairment (MCI), age-related cognitive decline, and memory loss resulting from the use of general anesthetics, chemotherapy, radiation treatment, post-surgical trauma, or therapeutic intervention; and diseases of the of the peripheral nervous system (PNS), including but not limited to, PNS neuropathies (e.g., vascular neuropathies, diabetic neuropathies, amyloid neuropathies, and the like), neuralgias, neoplasms, myelin-related diseases, etc.

[0357] Additionally, the disclosed methods provide for the application of a first neurogenic agent in combination with one or more other neurogenic agents to treat a subject or patient for a condition due to the anti-neurogenic effects of an opiate or opioid based analgesic. In some embodiments, the administration of an opiate or opioid based analgesic, such as an opiate like morphine or other opioid receptor agonist, to a subject or patient results in a decrease in, or inhibition of, neurogenesis. The administration of a first neurogenic agent in combination with one or more other neurogenic agents with an opiate or opioid based analgesic would reduce the anti-neurogenic effect. One non-limiting example is
administration of such a combination with an opioid receptor agonist after surgery (such as for the treating post-operative pain).

[0358] So the disclosed embodiments include a method of treating post operative pain in a subject or patient by combining administration of an opiate or opioid based analgesic with a first neurogenic agent in combination with one or more other neurogenic agents. The analgesic may have been administered before, simultaneously with, or after the combination. In some cases, the analgesic or opioid receptor agonist is morphine or another opiate.

[0359] Other disclosed embodiments include a method to treat or prevent decreases in, or inhibition of, neurogenesis in other cases involving use of an opioid receptor agonist. The methods comprise the administration of a first neurogenic agent in combination with one or more other neurogenic agents as described herein. Non-limiting examples include cases involving an opioid receptor agonist, which decreases or inhibits neurogenesis, and drug addiction, drug rehabilitation, and/or prevention of relapse into addiction. In some embodiments, the opioid receptor agonist is morphine, opium or another opiate.

[0360] Combinations and compositions disclosed herein can also be used to treat diseases of the peripheral nervous system (PNS), including but not limited to, PNS neuropathies (e.g., vascular neuropathies, diabetic neuropathies, amyloid neuropathies, and the like), neuralgias, neoplasms, myelin-related diseases, etc.


[0362] In some embodiments, a disclosed method may be used to moderate, alleviate, or otherwise treat a mood disorder in a subject or patient as described herein. Thus, in some embodiments, the disclosure includes a method of treating a mood disorder in such a subject or patient. Non-limiting examples of the method include those comprising administering a first neurogenic agent, or a combination thereof with one or more other neurogenic agents, to a subject or patient that is under treatment with a therapy and/or condition that results in a mood disorder. The administration may be with any combination and/or amount that is effective to produce an improvement in the mood disorder.
Representative and non-limiting mood disorders are described herein. Non-limiting examples of mood disorders include depression, major depression, treatment refractory depression, post-traumatic stress disorder (PTSD), anxiety, hypomania, panic attacks, excessive elation, seasonal mood (or affective) disorder, schizophrenia and other psychoses, lissencephaly syndrome, anxiety syndromes, anxiety disorders, phobias, stress and related syndromes, aggression, non-senile dementia, post-pain depression, and combinations thereof.

Increasing Neurodifferentiation

Certain embodiments herein provide a method of increasing neurodifferentiation of a cell or tissue, said method comprising administering to the cell or tissue a neurodifferentiating amount of either a composition, comprising an HMGCR modulating agent; and a second neurogenic agent, wherein the first and second agents are in combination in a single formulation.

In certain embodiments, the cell or the tissue is in a non-human mammalian subject in need of increased neurodifferentiation.

In certain embodiments, the cell or the tissue is in a human subject in need of increased neurodifferentiation.

In certain embodiments, the contacting step is performed in vitro, in vivo, ex vivo, or any combination thereof.

In some embodiments, neurodifferentiation (or a neurogenic response in certain embodiments) includes the differentiation of neural cells along different potential lineages. In some embodiments, the differentiation of neural stem or progenitor cells is along a neuronal cell lineage to produce neurons. In other embodiments, the differentiation is along both neuronal and glial cell lineages. In additional embodiments, the disclosure further includes differentiation along a neuronal cell lineage to the exclusion of one or more cell types in a glial cell lineage. Non-limiting examples of glial cell types include oligodendrocytes and radial glial cells, as well as astrocytes, which have been reported as being of an "astroglial lineage". Therefore, embodiments of the disclosure include differentiation along a neuronal cell lineage to the exclusion of one or more cell types selected from oligodendrocytes, radial glial cells, and astrocytes.
Selectivity

[0369] In some embodiments, selectivity of an HMGCR modulating agent, optionally in combination with one or more other neurogenic agents, is individually measured as the ratio of the IC$_{50}$ or EC$_{50}$ value for a desired effect (e.g., modulation of a neurogenic effect) relative to the IC$_{50}$/EC$_{50}$ value for an undesired effect. In some embodiments, a "selective" agent in a has a selectivity of less than about 1:2, less than about 1:10, less than about 1:50, or less than about 1:100. In some embodiments, one or more neurogenic agents individually exhibits selective activity in one or more organs, tissues, and/or cell types relative to another organ, tissue, and/or cell type. For example, in some embodiments, an agent in a combination selectively modulates neurogenesis in a known neurogenic region of the adult brain, such as the hippocampus (e.g., the dentate gyrus), the subventricular zone, and/or the olfactory bulb.

[0370] In certain embodiments, modulation by a combination of agents is in a region containing neural cells affected by disease or injury, a region containing neural cells associated with disease effects or processes, or a region containing neural cells which affect other events that are injurious to neural cells. Non-limiting examples of such events include stroke or radiation therapy of the region. In additional embodiments, a neurogenic combination substantially modulates two or more physiological activities or target molecules, while being substantially inactive against one or more other molecules and/or activities.

Indirect Action

[0371] In some embodiments, a neurogenic agent or combination thereof, as used herein, includes a neuromodulating agent that elicits an observable neurogenic response by producing, generating, stabilizing, or increasing the retention of an intermediate agent which, results in the neurogenic response. As used herein, "increasing the retention of" or variants of that phrase or the term "retention" refer to decreasing the degradation of, or increasing the stability of, an intermediate agent.

Benefits of Combinations

[0372] In some embodiments, an HMGCR modulating agent in combination with one or more other neurogenic agents results in improved efficacy, fewer side effects, a decrease in the severity of side effects, lower toxicity, lower effective dosages in one or both actives, less frequent dosing, and/or other desirable effects relative to use of the neurogenesis modulating
agents individually (such as at higher doses when used individually). Without being bound by
theory these benefits of the combinations may, e.g., be due to enhanced or synergistic
activities and/or the targeting of molecules and/or activities that are differentially expressed
in particular tissues and/or cell-types. Preferably, the neurogenic agent, in combination, has a
lower dosage than when used or administered alone.

Therapeutically Effective Amount

[0373] In certain embodiments, the amount of a combination of one or more neurogenic
agents disclosed herein may be an amount that also potentiates or sensitizes, such as by
activating or inducing cells to differentiate, a population of neural cells for neurogenesis. The
degree of potentiation or sensitization for neurogenesis may be determined with use of the
combination in any appropriate neurogenesis assay, including, but not limited to, a neuronal
differentiation assay described herein. In some embodiments, the amount of a neurogenic
agents is based on the highest amount of one agent in a combination, which amount produces
no detectable neuroproliferation in vitro but yet produces neurogenesis, or a measurable shift
in efficacy in promoting neurogenesis in vitro, when used in the combination. In certain
embodiments, the amount of first neurogenic agent and/or other agent(s) in a combination
used in vivo may be about 50%, about 45%, about 40%, about 35%, about 30%, about 25%,
about 20%, about 18%, about 16%, about 14%, about 12%, about 10%, about 8%, about 6%,
about 4%, about 2%, or about 1% or less than the maximum tolerated dose for a subject.
Non-limiting examples of subjects include both human beings and non-human mammals in
assays for behavior linked to neurogenesis. Exemplary animal assays are known to the skilled
person in the field.

[0374] In certain embodiments, the amount of a combination of a first neurogenic agent
and one or more other neurogenic agents may be an amount selected to be effective to
produce an improvement in a treated subject based on detectable neurogenesis in vitro as
described above. In some embodiments, such as in the case of a known neurogenic agent in a
combination of the disclosure, the amount is one that minimizes clinical side effects seen
with administration of the agent to a subject. The amount of an agent used in vivo may be
about 50%, about 45%, about 40%, about 35%, about 30%, about 25%, about 20%, about
18%, about 16%, about 14%, about 12%, about 10%, about 8%, about 6%, about 4%, about
2%, or about 1% or less of the maximum tolerated dose in terms of acceptable side effects for
a subject. This is readily determined for each agent(s) of a combination disclosed herein as well as those that have been in clinical use or testing, such as in humans.

[0375] In certain other embodiments, the amount of an additional neurogenic sensitizing agent in a combination of the disclosure is the highest amount which produces no detectable neurogenesis in vitro, including in animal (or non-human) models for behavior linked to neurogenesis, but yet produces neurogenesis, or a measurable shift in efficacy in promoting neurogenesis in the in vitro assay, when used in combination with a first neurogenic agent. Alternative embodiments include amounts which produce about 1%, about 2%, about 4%, about 6%, about 8%, about 10%, about 12%, about 14%, about 16%, about 18%, about 20%, about 25%, about 30%, about 35%, or about 40% or more of the neurogenesis seen with the amount that produces the highest level of neurogenesis in an in vitro assay.

[0376] As described herein, certain disclosed embodiments include methods of using a first neurogenic agent in combination with one or more other neurogenic agents at a level at which neurogenesis occurs. In certain embodiments, the amount of a first neurogenic agent in combination with one or more other neurogenic agents may be any that is effective to produce neurogenesis, optionally with reduced or minimized amounts of astrogenesis. In some embodiments, the amount may be the lowest needed to produce a desired, or minimum, level of detectable neurogenesis or beneficial effect.

[0377] In certain embodiments, an effective amount of a neurogenic agent, or combination thereof, in the disclosed methods is an amount sufficient, when used as described herein, to stimulate or increase a neurogenic effect in the subject targeted for treatment when compared to the absence of the combination. An effective amount of a combination may vary based on a variety of factors, including but not limited to, the activity of the active compounds, the physiological characteristics of the subject, the nature of the condition to be treated, and the route and/or method of administration all of which factors are understood by the skilled artisan. In certain embodiments, dosage ranges of certain compounds are provided herein and in the cited references based on animal models of CNS diseases and conditions. Various conversion factors, formulas, and methods for determining human dose equivalents of animal dosages are known in the art, and are described, e.g., in Freireich et al., Cancer Chemother Repts 50(4): 219 (1966), Monro et al., Toxicology Pathology, 23: 187-98 (1995), Boxenbaum and Dilea, J.Clin.Pharmacol. 35: 957-966 (1995), and Voisin et al., Reg. Toxicol. Pharmacol., 12(2): 107-116 (1990).
[0378] Certain embodiments provide of the administration of a first neurogenic agent or combination thereof in a dosage range of 0.001 ng/kg/day to 500 ng/kg/day, or in a dosage range of 0.05 to 200 ng/kg/day. However, as understood by those skilled in the art, the exact dosage of a first neurogenic agent, or combination thereof, used to treat a particular condition will vary in practice due to a wide variety of factors. Accordingly, dosage guidelines provided herein are not intended to be inclusive of the range of actual dosages, but rather provide guidance to skilled practitioners in selecting dosages useful in the empirical determination of dosages for individual patients. Advantageously, methods described herein allow treatment of one or more conditions with reductions in side effects, dosage levels, dosage frequency, treatment duration, safety, tolerability, and/or other factors.

[0379] The disclosed methods typically involve the administration of an HMGCR agent, optionally in combination with one or more other neurogenic agents, in a dosage range of from about 0.001 ng/kg/day to about 200 mg/kg/day. Other non-limiting dosages include from about 0.001 to about 0.01 ng/kg/day, about 0.01 to about 0.1 ng/kg/day, about 0.1 to about 1 ng/kg/day, about 1 to about 10 ng/kg/day, about 10 to about 100 ng/kg/day, about 100 ng/kg/day to about 1 µg/kg/day, about 1 to about 2 µg/kg/day, about 2 µg/kg/day to about 0.02 mg/kg/day, about 0.02 to about 0.2 mg/kg/day, about 0.2 to about 2 mg/kg/day, about 2 to about 20 mg/kg/day, or about 20 to about 200 mg/kg/day. However, as understood by those skilled in the art, the exact dosage of an HMGCR agent, optionally in combination with one or more other neurogenic agents, used to treat a particular condition will vary in practice due to a wide variety of factors. Accordingly, dosage guidelines provided herein are not limiting as the range of actual dosages, but rather provide guidance to skilled practitioners in selecting dosages useful in the empirical determination of dosages for individual patients. Advantageously, methods described herein allow treatment of one or more conditions with reductions in side effects, dosage levels, dosage frequency, treatment duration, safety, tolerability, and/or other factors. So where suitable dosages for an HMGCR agent to modulate an HMGCR activity are known to a skilled person, the disclosure includes the use of about 75%, about 50%, about 33%, about 25%, about 20%, about 15%, about 10%, about 5%, about 2.5%, about 1%, about 0.5%, about 0.25%, about 0.2%, about 0.1%, about 0.05%, about 0.025%, about 0.02%, about 0.01%, or less than the known dosage.

[0380] In other embodiments, the amount of an HMGCR agent used in vivo may be about 50%, about 45%, about 40%, about 35%, about 30%, about 25%, about 20%, about 18%, about 16%, about 14%, about 12%, about 10%, about 8%, about 6%, about 4%, about 2%, or
about 1% or less than the maximum tolerated dose for a subject, including where one or more other neurogenic agents is used in combination with the HMGCR agent. This is readily determined for each muscarinic agent that has been in clinical use or testing, such as in humans.

Alternatively, the amount of an HMGCR agent, optionally in combination with one or more other neurogenic agents, may be an amount selected to be effective to produce an improvement in a treated subject based on detectable neurogenesis in vitro as described above. In some embodiments, such as in the case of a known HMGCR agent, the amount is one that minimizes clinical side effects seen with administration of the agent to a subject. The amount of an agent used in vivo may be about 50%, about 45%, about 40%, about 35%, about 30%, about 25%, about 20%, about 18%, about 16%, about 14%, about 12%, about 10%, about 8%, about 6%, about 4%, about 2%, or about 1% or less of the maximum tolerated dose in terms of acceptable side effects for a subject. This is readily determined for each HMGCR agent or other agent(s) of a combination disclosed herein as well as those that have been in clinical use or testing, such as in humans.

In other embodiments, the amount of an additional neurogenic sensitizing agent in a combination with an HMGCR agent of the disclosure is the highest amount which produces no detectable neurogenesis in vitro, including in animal (or non-human) models for behavior linked to neurogenesis, but yet produces neurogenesis, or a measurable shift in efficacy in promoting neurogenesis in the in vitro assay, when used in combination with an HMGCR agent. Embodiments include amounts which produce about 1%, about 2%, about 4%, about 6%, about 8%, about 10%, about 12%, about 14%, about 16%, about 18%, about 20%, about 25%, about 30%, about 35%, or about 40% or more of the neurogenesis seen with the amount that produces the highest level of neurogenesis in an in vitro assay.

As described herein, the amount of an HMGCR agent, optionally in combination with one or more other neurogenic agents, may be any that is effective to produce neurogenesis, optionally with reduced or minimized amounts of astrogenesis. In some embodiments, the amount may be the lowest needed to produce a desired, or minimum, level of detectable neurogenesis or beneficial effect. Of course the administered HMGCR agent, alone or in a combination disclosed herein, may be in the form of a pharmaceutical composition.
In certain embodiments, the compositions disclosed herein are administered in the morning. In certain embodiments, the compositions disclosed herein are administered in the evening. In certain embodiments, the compositions disclosed herein are administered nocturnally.

In some embodiments, an effective, neurogenic amount of a combination of a composition of the present disclosure is an amount of the agent (or agents, in a combination) that achieves a concentration within the target tissue, using the particular mode of administration, at or above the IC$_{50}$ or EC$_{50}$ for activity of target molecule or physiological process. In some embodiments, a neurogenic agent, or combination thereof, is administered in a manner and dosage that gives a peak concentration of about 1, about 1.5, about 2, about 2.5, about 5, about 10, about 20 or more times the IC$_{50}$ or EC$_{50}$ concentration of one or more of the agents in the combination. Certain IC$_{50}$ and EC$_{50}$ values and bioavailability data for the agent(s) described herein are known in the art, and are described, e.g., in the references cited herein or can be readily determined using established methods. In addition, methods for determining the concentration of a free compound in plasma and extracellular fluids in the CNS, as well pharmacokinetic properties, are known in the art, and are described, e.g., in de Lange et al., AAPS Journal, 7(3):532-543 (2005). In some embodiments, a combination neurogenic agents described herein is administered as a combination in a single formulation or separate agents used together, at a frequency of at least about once daily, or about twice daily, or about three or more times daily, and for a duration of 1 day, or at least about 1 day, about 3 days, about 5 days, about 7 days, about 10 days, about 14 days, or about 21 days, or about 4 weeks, or about 2 months, or about 4 months, or about 6 months, or about 8 months, or about 10 months, or about 1 year, or about 2 years, or about 4 years, or about 6 years or longer.

In other embodiments, an effective, neurogenesis modulating amount is a dose that produces a concentration of a first neurogenic agent and/or other agent(s) of a combination in an organ, tissue, cell, and/or other region of interest that includes the ED$_{50}$ (the pharmacologically effective dose in 50% of subjects) with little or no toxicity. IC$_{50}$ and EC$_{50}$ values for the modulation of neurogenesis can be determined using methods described in U.S. Published Application No. 2007/0015138, or by other methods known in the art. In some embodiments, the IC$_{50}$ or EC$_{50}$ concentration for the modulation of neurogenesis is substantially lower than the IC$_{50}$ or EC$_{50}$ concentration for activity of a first neurogenic agent.
and/or other agent(s) of a combination at non-targeted molecules and/or physiological processes.

[0387] In other embodiments, an effective, neurogenesis modulating amount is a dose that produces a concentration of an HMGCR agent (or each agent in a combination) in an organ, tissue, cell, and/or other region of interest that includes the ED$_{50}$ (the pharmacologically effective dose in 50% of subjects) with little or no toxicity. IC$_{50}$ and EC$_{50}$ values for the modulation of neurogenesis can be determined using methods described in U.S. Provisional Application No. 60/697,905 to Barlow et al., filed July 8, 2005 (see, e.g., U.S. Published Application No. 2007/0015138) or by other methods known in the art. In some embodiments, the IC$_{50}$ or EC$_{50}$ concentration for the modulation of neurogenesis is substantially lower than the IC$_{50}$ or EC$_{50}$ concentration for activity of an HMGCR agent and/or other agent(s) at non-targeted molecules and/or physiological processes.

[0388] In some methods described herein, the application of an HMGCR agent in combination with one or more other neurogenic agents may allow effective treatment with substantially fewer and/or less severe side effects compared to existing treatments. In some embodiments, combination therapy with an HMGCR agent and one or more additional neurogenic agents allows the combination to be administered at dosages that would be subtherapeutic when administered individually or when compared to other treatments. In other embodiments, each agent in a combination of agents may be present in an amount that results in fewer and/or less severe side effects than that which occurs with a larger amount. Thus the combined effect of the neurogenic agents will provide a desired neurogenic activity while exhibiting fewer and/or less severe side effects overall. In further embodiments, methods described herein allow treatment of certain conditions for which treatment with the same or similar compounds is ineffective using known methods due, for example, to dose-limiting side effects, toxicity, and/or other factors.

**Pharmaceutically Acceptable Carrier**

[0389] In certain embodiments, a neurogenic agent, or combination thereof, is used in the methods described herein, in the form of a composition that includes at least one pharmaceutically acceptable carrier. As used herein, the term "pharmaceutically acceptable carrier" includes any excipient known in the field as suitable for pharmaceutical application to a mammal, preferably a human. Suitable pharmaceutical excipients and formulations are
known in the art and are described, for example, in Remington's Pharmaceutical Sciences (19th ed.) (Genarro, ed. (1995) Mack Publishing Co., Easton, Pa.). Preferably, pharmaceutical carriers are chosen based upon the intended mode of administration as is known to one skilled in the art. The pharmaceutically acceptable carrier may include, for example, disintegrants, binders, lubricants, glidants, emollients, humectants, thickeners, silicones, flavoring agents, physiologically balanced buffer, and water.

[0390] In certain embodiments, a neurogenic agent may be incorporated with excipients and administered in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, or any other form known in the pharmaceutical arts. The pharmaceutical compositions may also be formulated in a sustained release form in certain embodiments. Sustained release compositions, enteric coatings, and the like are known in the art. Alternatively, the compositions may be a quick release formulation in certain embodiments.

15 Certain Ex Vivo Methods

[0391] In other embodiments, methods described herein involve modulating neurogenesis ex vivo with a first neurogenic agent, optionally in combination with one or more other neurogenic agents, such that a composition containing neural stem cells, neural progenitor cells, and/or differentiated neural cells can subsequently be administered to an individual to treat a disease or condition. In some embodiments, the method of treatment comprises the steps of contacting a neural stem cell or progenitor cell with a first neurogenic agent, optionally in combination with one or more other neurogenic agents, to modulate neurogenesis, and transplanting the cells into a patient in need of treatment. Methods for transplanting stem and progenitor cells are known in the art, and are described, e.g., in U.S. Patent Nos. 5,928,947; 5,817,773; and 5,800,539, and PCT Publication Nos. WO 01/176507 and WO 01/170243. In some embodiments, methods described herein allow treatment of diseases or conditions by directly replenishing, replacing, and/or supplementing damaged or dysfunctional neurons. In further embodiments, methods described herein enhance the growth and/or survival of existing neural cells, and/or slow or reverse the loss of such cells in a neurodegenerative or other condition.

[0392] In certain alternative embodiments, the method of treatment comprises identifying, generating, and/or propagating neural cells ex vivo in contact with a first neurogenic agent,
optionally in combination with one or more other neurogenic agents, and transplanting the cells into a subject. In another embodiment, the method of treatment comprises the steps of contacting a neural stem cell or progenitor cell with one or more neurogenic agents to stimulate neurogenesis, and transplanting the cells into a patient in need of treatment. Also disclosed are methods for preparing a population of neural stem cells suitable for transplantation, comprising culturing a population of neural stem cells (NSCs) in vitro, and contacting the cultured neural stem cells with a neurogenic agent described herein. The disclosure further includes methods of treating the diseases, disorders, and conditions described herein by transplanting such cells into a subject or patient.

Neurogenesis with Angiogenesis

[0393] In additional embodiments, the disclosure includes a method of stimulating or increasing neurogenesis in a subject or patient with stimulation of angiogenesis in the subject or patient. The co-stimulation may be used to provide the differentiating and/or proliferating cells with increased access to the circulatory system. The neurogenesis is produced by modulation of HMGCR activity, such as with an HMGCR modulating agent (preferably an inhibitor), optionally in combination with one or more other neurogenic agents, as described herein. An increase in angiogenesis may be mediated by a means known to the skilled person, including administration of an angiogenic factor or treatment with an angiogenic therapy. Non-limiting examples of angiogenic factors or conditions include vascular endothelial growth factor (VEGF), angiopoietin-1 or -2, erythropoietin, exercise, or a combination thereof.

[0394] So in some embodiments, the disclosure includes a method comprising administering i) an HMGCR agent, optionally in combination with one or more other neurogenic agents, and ii) one or more angiogenic factors to a subject or patient. In other embodiments, the disclosure includes a method comprising administering i) an HMGCR agent, optionally in combination with one or more other neurogenic agents, to a subject or patient with ii) treating said subject or patient with one or more angiogenic conditions. The subject or patient may be any as described herein.

[0395] The co-treatment of a subject or patient includes simultaneous treatment or sequential treatment as non-limiting examples. In cases of sequential treatment, the administration of an HMGCR agent, optionally with one or more other neurogenic agents, may be before or after the administration of an angiogenic factor or condition. Of course in
the case of a combination of an HMGCR agent and one or more other neurogenic agents, the
HMGCR agent may be administered separately from the one or more other agents, such that
the one or more other agent is administered before or after administration of an angiogenic
factor or condition.

5

Methods of Delivery
[0396] Certain embodiments, disclose methods comprising contacting a cell with an
HMGCR agent, optionally in combination with one or more other neurogenic agents, or
administering such an agent or combination to a subject, to result in neurogenesis. Some
embodiments comprise the use of one HMGCR agent in combination with one or more other
neurogenic agents.

[0397] In some embodiments, methods of treatment comprise the step of administering to a
mammal an HMGCR agent, optionally in combination with one or more other neurogenic
agents, for a time and at a concentration sufficient to treat the condition targeted for
treatment. The disclosed methods can be applied, for example, to individuals having, or who
are likely to develop, disorders relating to neural degeneration, neural damage and/or neural
demyelination.

[0398] Depending on the desired clinical result, the disclosed combinations of agents or
pharmaceutical compositions are administered by any means suitable for achieving a desired
effect. Various delivery methods are known in the art and can be used to deliver an agent to a
subject or to NSCs or progenitor cells within a tissue of interest. The delivery method will
depend on factors such as the tissue of interest, the nature of the compound (e.g., its stability
and ability to cross the blood-brain barrier), and the duration of the experiment or treatment,
among other factors. For example, an osmotic minipump can be implanted into a neurogenic
region, such as the lateral ventricle. Alternatively, compounds can be administered by direct
injection into the cerebrospinal fluid of the brain or spinal column, or into the eye.
Compounds can also be administered into the periphery (such as by intravenous or
subcutaneous injection, or oral delivery), and subsequently cross the blood-brain barrier.

[0399] In various embodiments, the disclosed agents or pharmaceutical compositions are
administered in a manner that allows them to contact the subventricular zone (SVZ) of the
lateral ventricles and/or the dentate gyrus of the hippocampus. Examples of routes of
administration include parenteral, e.g., intravenous, intradermal, subcutaneous, oral (e.g.,
inhalation), transdermal (topical), transmucosal, and rectal administration. Intranasal administration generally includes, but is not limited to, inhalation of aerosol suspensions for delivery of compositions to the nasal mucosa, trachea and bronchioli.

[0400] In some embodiments, disclosed agents or pharmaceutical compositions are administered so as to either pass through or by-pass the blood-brain barrier. Methods for allowing factors to pass through the blood-brain barrier are known in the art, and include minimizing the size of the factor, providing hydrophobic factors which facilitate passage, and conjugation to a carrier molecule that has substantial permeability across the blood brain barrier. In some instances, the combination of compounds can be administered by a surgical procedure implanting a catheter coupled to a pump device. The pump device can also be implanted or be extracorporally positioned. Administration of a combination of disclosed agents or pharmaceutical compositions can be in intermittent pulses or as a continuous infusion. Devices for injection to discrete areas of the brain are known in the art. In certain embodiments, the combination is administered locally to the ventricle of the brain, substantia nigra, striatum, locus ceruleous, nucleus basalis Meynert, pedunculopontine nucleus, cerebral cortex, and/or spinal cord by, e.g., injection. Methods, compositions, and devices for delivering therapeutics, including therapeutics for the treatment of diseases and conditions of the CNS and PNS, are known in the art.

[0401] In some embodiments, a neurogenic agent, or combination thereof, as described herein is modified to facilitate crossing of the gut epithelium. For example, in some embodiments, disclosed agents or pharmaceutical compositions are a prodrug wherein the prodrug form is actively transported across the intestinal epithelium and metabolized into the active agent in systemic circulation and/or in the CNS.

[0402] In some embodiments, the delivery or targeting of disclosed agents or pharmaceutical compositions to a neurogenic region, such as the dentate gyrus or the subventricular zone, enhances efficacy and reduces side effects compared to known methods involving administration with the same or similar compounds.

[0403] In other embodiments, disclosed agents or pharmaceutical compositions are conjugated to a targeting domain to form a chimeric therapeutic, where the targeting domain facilitates passage of the blood-brain barrier (as described above) and/or binds one or more molecular targets in the CNS. In some embodiments, the targeting domain binds a target that is differentially expressed or displayed on, or in close proximity to, tissues, organs, and/or
cells of interest. In some cases, the target is preferentially distributed in a neurogenic region of the brain, such as the dentate gyrus and/or the SVZ. For example, in some embodiments, a neurogenic agent, or combination thereof, as described herein is conjugated or complexed with the fatty acid docosahexaenoic acid (DHA), which is readily transported across the blood brain barrier and imported into cells of the CNS.

**Identifying a Patient in Need of Treatment**

[0404] In embodiments to treat non-human mammals and/or human patients, the methods include identifying a patient suffering from one or more disease, disorders, or conditions, or a symptom thereof, and administering to the subject or patient a neurogenic agent, or combination thereof, as described herein. The identification of a subject or patient as having one or more disease, disorder or condition, or a symptom thereof, may be made by a skilled practitioner (non-limiting examples include, a physician or a psychologist) using any appropriate means known in the field.

[0405] In some embodiments, identifying a patient in need of a neurogenic response comprises identifying a patient who has or will be exposed to a factor or condition known to inhibit neurogenesis, including but not limited to, stress, aging, sleep deprivation, hormonal changes (e.g., those associated with puberty, pregnancy, or aging (e.g., menopause), lack of exercise, lack of environmental stimuli (e.g., social isolation), diabetes and drugs of abuse (e.g., alcohol, especially chronic use; opiates and opioids; psychostimulants). In some embodiments, the patient has been identified as non-responsive to treatment with primary medications for the condition(s) targeted for treatment (e.g., non-responsive to antidepressants for the treatment of depression), and the a neurogenic agent, or combination thereof, as described herein is administered in a method for enhancing the responsiveness of the patient to a co-existing or pre-existing treatment regimen.

[0406] In certain embodiments, the method or treatment comprises administering a combination of a primary medications for the condition(s) targeted for treatment and a first neurogenic agent, optionally in combination with one or more other neurogenic agents. For example, in the treatment of depression or related neuropsychiatric disorders, a combination may be administered in conjunction with, or in addition to, electroconvulsive shock treatment, a monoamine oxidase modulator, and/or a selective reuptake modulators of serotonin and/or norepinephrine.
In certain embodiments, the patient in need of neurogenesis modulation suffers from premenstrual syndrome, post-partum depression, or pregnancy-related fatigue and/or depression, and the treatment comprises administering a therapeutically effective amount of a neurogenic agent, or combination thereof, as described herein. Without being bound by any particular theory, and offered to improve understanding of the invention, it is believed that levels of steroid hormones, such as estrogen, are increased during the menstrual cycle during and following pregnancy, and that such hormones can exert a modulatory effect on neurogenesis.

In some embodiments, the patient is a user of a recreational drug including but not limited to alcohol, amphetamines, PCP, cocaine, and opiates. Without being bound by any particular theory, and offered to improve understanding of the invention, it is believed that some drugs of abuse have a modulatory effect on neurogenesis, which is associated with depression, anxiety and other mood disorders, as well as deficits in cognition, learning, and memory. Moreover, mood disorders are causative/risk factors for substance abuse, and substance abuse is a common behavioral symptom (e.g., self medicating) of mood disorders. Thus, substance abuse and mood disorders may reinforce each other, rendering patients suffering from both conditions non-responsive to treatment. Thus, in some embodiments, a neurogenic agent, or combination thereof, as described herein is used to treat patients suffering from substance abuse and/or mood disorders. In various embodiments, the one or more additional agents can be an antidepressant, an antipsychotic, a mood stabilizer, or any other agent known to treat one or more symptoms exhibited by the patient. In some embodiments, a neurogenesis modulating agent exerts a synergistic effect with one or more additional agents on the treatment of substance abuse and/or mood disorders in patients suffering from both conditions.

In further embodiments, the patient is on a co-existing and/or pre-existing treatment regimen involving administration of one or more prescription medications having a modulatory effect on neurogenesis. For example, in some embodiments, the patient suffers from chronic pain and is prescribed one or more opiate/opioid medications; and/or suffers from ADD, ADHD, or a related disorder, and is prescribed a psychostimulant, such as ritalin, dextedrine, adderall, or a similar medication which inhibits neurostimulation. Without being bound by any particular theory, and offered to improve understanding of the invention, it is believed that such medications can exert a modulatory effect on neurogenesis, leading to depression, anxiety and other mood disorders, as well as deficits in cognition, learning, and
memory. Thus, in some preferred embodiments, a neurogenic agent, or combination thereof, as described herein is administered to a patient who is currently or has recently been prescribed a medication that exerts a modulatory effect on neurogenesis, in order to treat depression, anxiety, and/or other mood disorders, and/or to improve cognition.

[0410] In additional embodiments, the patient suffers from chronic fatigue syndrome; a sleep disorder; lack of exercise (e.g., elderly, infirm, or physically handicapped patients); and/or lack of environmental stimuli (e.g., social isolation); and the treatment comprises administering a therapeutically effective amount of a neurogenic agent, or combination thereof, as described herein.

[0411] In more embodiments, the patient is an individual having, or who is likely to develop, a disorder relating to neural degeneration, neural damage and/or neural demyelination.

[0412] In certain embodiments, identifying a patient in need of neurogenesis modulation comprises selecting a population or sub-population of patients, or an individual patient, that is more amenable to treatment and/or less susceptible to side effects than other patients having the same disease or condition. In some embodiments, identifying a patient amenable to treatment with a neurogenic agent, or combination thereof, as described herein comprises identifying a patient who has been exposed to a factor known to enhance neurogenesis, including but not limited to, exercise, hormones or other endogenous factors, and drugs taken as part of a pre-existing treatment regimen. In some embodiments, a sub-population of patients is identified as being more amenable to neurogenesis modulation with a neurogenic agent, or combination thereof, as described herein by taking a cell or tissue sample from prospective patients, isolating and culturing neural cells from the sample, and determining the effect of the combination on the degree or nature of neurogenesis of the cells, thereby allowing selection of patients for which the therapeutic agent has a substantial effect on neurogenesis. Advantageously, the selection of a patient or population of patients in need of or amenable to treatment with a combination of the disclosure allows more effective treatment of the disease or condition targeted for treatment than known methods using the same or similar compounds.

[0413] In some embodiments, the patient has suffered a CNS insult, such as a CNS lesion, a seizure (e.g., electroconvulsive seizure treatment; epileptic seizures), radiation, chemotherapy and/or stroke or other ischemic injury. Without being bound by any particular
theory, and offered to improve understanding of the invention, it is believed that some CNS
insults/injuries leads to increased proliferation of neural stem cells, but that the resulting
neural cells form aberrant connections which can lead to impaired CNS function and/or
diseases, such as temporal lobe epilepsy. In other embodiments, a neurogenic agent, or
combination thereof, as described herein is administered to a patient who has suffered, or is at
risk of suffering, a CNS insult or injury to stimulate neurogenesis. Advantageously,
stimulation of the differentiation of neural stem cells with a neurogenic agent, or combination
thereof, as described herein activates signaling pathways necessary for progenitor cells to
effectively migrate and incorporate into existing neural networks or to block inappropriate
proliferation.

[0414] In further embodiments, the methods may be used to treat a cell, tissue, or subject
which is exhibiting decreased neurogenesis or increased neurodegeneration. In some
embodiments, the cell, tissue, or subject is, or has been, subjected to, or contacted with, an
agent that decreases or inhibits neurogenesis. One non-limiting example is a human subject
that has been administered morphine or other agent which decreases or inhibits neurogenesis.
Non-limiting examples of other agents include opiates and opioid receptor agonists, such as
mu receptor subtype agonists, that inhibit or decrease neurogenesis.

[0415] Thus in additional embodiments, the methods may be used to treat subjects having,
or diagnosed with, depression or other withdrawal symptoms from morphine or other agents
which decrease or inhibit neurogenesis. This is distinct from the treatment of subjects having,
or diagnosed with, depression independent of an opiate, such as that of a psychiatric nature,
as disclosed herein. In further embodiments, the methods may be used to treat a subject with
one or more chemical addiction or dependency, such as with morphine or other opiates,
where the addiction or dependency is ameliorated or alleviated by an increase in

neurogenesis.

Assays

[0416] Assays for detecting and measuring neurogenesis, a neurogenic response, and
neurodifferentiation (including as qualitative and quantitative measurements) are known in
the art (see, for example, PCT Application No. US2006/026677 published as
WO2007008758 which also discloses tools and methods for identifying populations of neural
stem cells suitable for transplantation).
In one non-limiting example neurogenesis, a neurogenic response, and neurodifferentiation are all measured in an in vitro assay as follows. Human neural stem cells (hNSCs) are isolated and grown in monolayer culture, plated, treated with varying concentrations of a first neurogenic agent, or a combination of a first neurogenic agent with one or more additional neurogenic agents (test compound), and stained with TUJ-I antibody to identify neurons and/or GFAP to identify astrocytes, as described in PCT Application No. US06/026677. Mitogen-free test media with a positive control is used for neuronal differentiation, and basal media without growth factors serves as a negative control. Neurogenesis is determined, for example, by measuring the proliferation and/or differentiation of the hNSCs in the presence of varying concentrations of test compound compared to the absence of the test compound (negative control). A neurogenic response is measured, for example, in a similar manner to neurogenesis, except that astrogenesis is also measured and the ratio of neurogenesis to astrogenesis is determined to measure the neurogenic response. Neurodifferentiation is measured, for example, by detecting neurodifferentiation specific expression markers which methods are known in the art.

EXAMPLES

Example 1 - Effect of atorvastatin on neuronal differentiation of human neural stem cells

Human neural stem cells (hNSCs) were isolated and grown in monolayer culture, plated, treated with varying concentrations of atorvastatin (test compound), and stained with TUJ-I antibody, as described in U.S. Provisional Application No. 60/697,905 (U.S. Patent Publication 2007/0015138). Mitogen-free test media with a positive control for neuronal differentiation was used along with basal media without growth factors as a negative control.

Results are shown in Figure 1, which shows dose response curves of neuronal differentiation after background media values are subtracted. The dose response curve of the neuronal positive control is included as a reference. The data is presented as a percent of neuronal positive control. The data indicate that atorvastatin promoted neuronal differentiation.
Example 2 - Effects of the 5-HT1a agonist Buspirone in combination with the HMGCR inhibitor atorvastatin on differentiation of human neural stem cells

[0420] Human neural stem cells (hNSCs) were isolated and grown in monolayer culture, plated, treated with varying concentrations of atorvastatin in the presence or absence of buspirone, and stained with TUJ-I antibody for the detection of neuronal differentiation or GFAP antibody for the detection of astrocyte differentiation, as described in U.S. Provisional Application No. 60/697,905 (U.S. Patent Publication 2007/0015138). Mitogen-free test media with a positive control for neuronal differentiation was used along with basal media without growth factors as a negative control.

[0421] Results are shown in Figure 2, which shows concentration response curves of neuronal differentiation after background media values are subtracted. The concentration response curves of the combination of atorvastatin with buspirone are shown with the concentration response curves either agent alone. The data is presented as a percent of neuronal positive control. The data indicate that the combination of atorvastatin with buspirone resulted in synergistically enhanced neuronal differentiation relative to that produced by either agent alone.

Example 3 - Effects of the antiviral agent and IMPDH inhibitor Ribavirin in combination with the HMGCR inhibitor atorvastatin on differentiation of human neural stem cells

[0422] Human neural stem cells (hNSCs) were isolated and grown in monolayer culture, plated, treated with varying concentrations of atorvastatin in the presence or absence of ribavirin, and stained with TUJ-I antibody for the detection of neuronal differentiation or GFAP antibody for the detection of astrocyte differentiation, as described in U.S. Provisional Application No. 60/697,905 (U.S. Patent Publication 2007/0015138). Mitogen-free test media with a positive control for neuronal differentiation was used along with basal media without growth factors as a negative control.

[0423] Results are shown in Figure 3, which shows concentration response curves of neuronal differentiation after background media values are subtracted. The concentration response curves of the combination of atorvastatin with ribavirin are shown with the concentration response curves either agent alone. The data is presented as a percent of neuronal positive control. The data indicate that the combination of atorvastatin with ribavirin
resulted in synergistically enhanced neuronal differentiation relative to that produced by either agent alone.

Example 4 - Effects of the acetylcholinesterase inhibitor Tacrine in combination with the HMGCR inhibitor atorvastatin on differentiation of human neural stem cells

Human neural stem cells (hNSCs) were isolated and grown in monolayer culture, plated, treated with varying concentrations of atorvastatin in the presence or absence of tacrine, and stained with TUJ-I antibody for the detection of neuronal differentiation or GFAP antibody for the detection of astrocyte differentiation, as described in U.S. Provisional Application No. 60/697,905 (U.S. Patent Publication 2007/0015138). Mitogen-free test media with a positive control for neuronal differentiation was used along with basal media without growth factors as a negative control.

Results are shown in Figure 4, which shows concentration response curves of neuronal differentiation after background media values are subtracted. The concentration response curves of the combination of atorvastatin with tacrine are shown with the concentration response curves either agent alone. The data is presented as a percent of neuronal positive control. The data indicate that the combination of atorvastatin with tacrine resulted in synergistically enhanced neuronal differentiation relative to that produced by either agent alone.

Example 5 - Effects of the GSK3β inhibitor Azakenpaullone in combination with the HMGCR inhibitor atorvastatin on differentiation of human neural stem cells

Human neural stem cells (hNSCs) were isolated and grown in monolayer culture, plated, treated with varying concentrations of atorvastatin in the presence or absence of azakenpaullone, and stained with TUJ-I antibody for the detection of neuronal differentiation or GFAP antibody for the detection of astrocyte differentiation, as described in U.S. Provisional Application No. 60/697,905 (U.S. Patent Publication 2007/0015138). Mitogen-free test media with a positive control for neuronal differentiation was used along with basal media without growth factors as a negative control.

Results are shown in Figure 5, which shows concentration response curves of neuronal differentiation after background media values are subtracted. The concentration
response curves of the combination of atorvastatin with azakenpaullone are shown with the concentration response curves either agent alone. The data is presented as a percent of neuronal positive control. The data indicate that the combination of atorvastatin with azakenpaullone resulted in synergistically enhanced neuronal differentiation relative to that produced by either agent alone.

**Example 6 - Effects of the folic acid in combination with the HMGCR inhibitor atorvastatin on differentiation of human neural stem cells**

[0428] Human neural stem cells (hNSCs) were isolated and grown in monolayer culture, plated, treated with varying concentrations of atorvastatin in the presence or absence of folic acid, and stained with TUJ-I antibody for the detection of neuronal differentiation or GFAP antibody for the detection of astrocyte differentiation, as described in U.S. Provisional Application No. 60/697,905 (U.S. Patent Publication 2007/0015138). Mitogen-free test media with a positive control for neuronal differentiation was used along with basal media without growth factors as a negative control.

[0429] Results are shown in Figure 6, which shows concentration response curves of neuronal differentiation after background media values are subtracted. The concentration response curves of the combination of atorvastatin with folic acid are shown with the concentration response curves either agent alone. The data is presented as a percent of neuronal positive control. The data indicate that the combination of atorvastatin with folic acid resulted in synergistically enhanced neuronal differentiation relative to that produced by either agent alone.

**Example 7 - Effects of the serotonin reuptake model serotonin in combination with the HMGCR inhibitor atorvastatin on differentiation of human neural stem cells**

[0430] Human neural stem cells (hNSCs) were isolated and grown in monolayer culture, plated, treated with varying concentrations of atorvastatin in the presence or absence of serotonin, and stained with TUJ-I antibody for the detection of neuronal differentiation or GFAP antibody for the detection of astrocyte differentiation, as described in U.S. Provisional Application No. 60/697,905 (U.S. Patent Publication 2007/0015138). Mitogen-free test media with a positive control for neuronal differentiation was used along with basal media without growth factors as a negative control.
[0431] Results are shown in Figure 7, which shows concentration response curves of neuronal differentiation after background media values are subtracted. The concentration response curves of the combination of atorvastatin with serotonin are shown with the concentration response curves either agent alone. The data is presented as a percent of neuronal positive control. The data indicate that the combination of atorvastatin with serotonin resulted in synergistically enhanced neuronal differentiation relative to that produced by either agent alone.

Example 8 - Effects of atorvastatin in combination with fluoxetine on in vivo rat neurogenesis

[0432] Male F344 rats were dosed 1x per day for 21-days with 0 (vehicle only), 5.0 mg/kg fluoxetine (n = 12 per dose group, p.o.), 15.0 mg/kg fluoxetine (n = 12 per dose group, p.o.), 10.0 mg/kg atorvastatin (n = 12 per dose group, p.o.) or the combination of fluoxetine (5.0 mg/kg, p.o.) + atorvastatin (10.0 mg/kg, p.o.). BrdU was administered once daily between days 9 and 14 (100 mg/kg/day, i.p., n=12 per dose group). Figure 8 shows BrdU positive cell counts within the granule cell layer of the dentate gyrus. Data are presented as percent change in BrdU positive cells per cubic mm dentate gyrus. Atorvastatin alone significantly increased the number of BrdU positive cells. Figure 9 shows the rate of neuronal differentiation of BrdU+ cells within the granule cell layer of the dentate gyrus. Data are presented as the percentage of cells colabeled for BrdU and the mature neuronal marker NeuN within the dentate gyrus. The combination of atorvastatin + fluoxetine resulted in a significant increase in the percentage of BrdU+/NeuN+ cells. Figure 10 shows the number of new neurons within the granule cell layer of the dentate gyrus. Both atorvastatin alone and the combination of atorvastatin with fluoxetine resulted in a significant increase in the number of new neurons.

[0433] Each foreign patent and U.S. patent, published patent application, journal article, and other citation listed herein is incorporated herein by reference in its entirety.

[0434] Having now fully provided the instant disclosure, it will be appreciated by those skilled in the art that the same can be performed within a wide range of equivalent parameters, concentrations, and conditions without departing from the spirit and scope of the disclosure and without undue experimentation.

[0435] While the disclosure has been described in connection with specific embodiments thereof, it will be understood that it is capable of further modifications. This application is
intended to cover any variations, uses, or adaptations of the disclosure following, in general, the disclosed principles and including such departures from the disclosure as come within known or customary practice within the art to which the disclosure pertains and as may be applied to the essential features hereinbefore set forth.
WHAT IS CLAIMED IS:

1. A composition, comprising:
   a) a first neurogenic agent comprising an inhibitor of 3-hydroxy-3-methyl-glutaryl-CoA reductase (HMGCR); and
   b) a second neurogenic agent, wherein the first and second agents are in combination in a single formulation, and wherein the second agent is not an antidepressant.

2. The composition of claim 1, further comprising a pharmaceutically acceptable carrier.

3. The composition of claim 1, wherein the first and second agents are combined together in a unit dose.

4. The composition of claim 1, wherein the first neurogenic agent is an inhibitor of HMGCR; and
   the second agent is a muscarinic receptor modulator, a phosphodiesterase (PDE) modulator, histone deacetylase (HDAC) modulator, a gamma-aminobutyric acid (GABA) receptor modulator, a thyrotropin-releasing hormone (TRH) receptor agonist, a weight modulating agent, a glutamate receptor modulator, an amphetamine, a peroxisome proliferator-activated receptor (PPAR) modulator, a nootropic, an alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) receptor modulator, an opioid receptor modulator, an androgen receptor modulating agent, a rho kinase inhibitor, a glycogen synthase kinase 3 (GSK-3) modulating agent, an acetylcholinesterase (AChE) inhibitor, an epilepsy treating agent, a dual sodium and calcium channel modulating agent, a calcium channel modulating agent, a melanocortin receptor modulating agent, an angiotensin II receptor modulating agent, a neurosteroid agent, a non-steroidal anti-inflammatory agent, a migraine treating agent, a nuclear hormone receptor modulating agent, a nicotinic receptor modulating agent, a cannabinoid receptor modulating agent, a fatty acid amide hydrolase (FAAH) antagonist, a nitric oxide modulating agent, a prolactin modulating agent, an antiviral agent, a calcitonin receptor agonist, an antioxidant agent, a norepinephrine receptor modulating agent, a carbonic anhydrase modulating agent, a catechol-o-methyltransferase (COMT) modulating agent, a hedgehog modulating agent, an inosine monophosphate dehydrogenase (IMPDH) modulating agent, or a sigma receptor modulating agent.
5. The composition of claim 1, wherein the first neurogenic agent is atorvastatin (CAS RN 134523-00-5), cerivastatin (CAS RN 145599-86-6), crilvastatin (CAS RN 120551-59-9), fluvastatin (CAS RN 93957-54-1), fluvastatin sodium (CAS RN 93957-55-2), simvastatin (CAS RN 79902-63-9), lovastatin (CAS RN 75330-75-5), pravastatin (CAS RN 81093-37-0), pravastatin sodium (CAS RN 81131-70-6), rosuvastatin (CAS RN 287714-41-4), or simvastatin (CAS RN 79902-63-9); and

the second agent is a thyrotropin-releasing hormone (TRH) receptor agonist, a weight modulating agent, a glutamate receptor modulator, an amphetamine, a peroxisome proliferator-activated receptor (PPAR) modulator, a nootropic agent, an α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) receptor modulator, an opioid receptor modulator, an androgen receptor modulating agent, a rho kinase inhibitor, a glycogen synthase kinase 3 (GSK-3) modulating agent, an acetylcholinesterase (AChE) inhibitor, an epilepsy treating agent, a dual sodium and calcium channel modulating agent, a calcium channel modulating agent, a melanocortin receptor modulating agent, an angiotensin II receptor modulating agent, a neurosteroid agent, a non-steroidal anti-inflammatory agent, a migraine treating agent, a nuclear hormone receptor modulating agent, a nicotinic receptor modulating agent, a cannabinoid receptor modulating agent, a fatty acid amide hydrolase (FAAH) antagonist, a nitric oxide modulating agent, a prolactin modulating agent, an antiviral agent, a calcitonin receptor agonist, an antioxidant agent, a norepinephrine receptor modulating agent, a carbonic anhydrase modulating agent, a catechol-o-methyltransferase (COMT) modulating agent, a hedgehog modulating agent, an inosine monophosphate dehydrogenase (IMPDH) modulating agent, or a sigma receptor modulating agent.

6. The composition of claim 1, wherein the second neurogenic agent has the property of enhancing a neurogenic effect of the first neurogenic agent.

7. The composition of claim 1, wherein the first and the second agents act synergistically.

8. A composition comprising a first neurogenic agent and a second neurogenic agent in combination in a single formulation, wherein the first agent is an inhibitor of 3-hydroxy-3-methyl-glutaryl-CoA reductase (HMGCR); and the second agent is a selective serotonin reuptake inhibitor (SSRI).
9. The composition of claim 8, wherein the first neurogenic agent is atorvastatin (CAS RN 134523-00-5); and the second neurogenic agent is the SSRI.

10. The composition of claim 9, wherein the first neurogenic agent is atorvastatin; and the second neurogenic agent is fluoxetine, duloxetine, sertraline, paroxetine, fluvoxamine, citalopram, or escitalopram.

11. A composition comprising a first neurogenic agent and a second neurogenic agent combined in a single formulation, wherein the first neurogenic agent is an inhibitor of 3-hydroxy-3-methyl-glutaryl-CoA reductase (HMGCR); and the second neurogenic agent is a 5-HT1a agonist, an antiviral agent, an acetylcholinesterase inhibitor, a GSK-3 inhibitor, or a one-carbon metabolism modulator.

12. The composition of claim 11, wherein the first neurogenic agent is an inhibitor of 3-hydroxy-3-methyl-glutaryl-CoA reductase (HMGCR); and the second neurogenic agent is buspirone, ribavirin, tacrine, azakenpaullone, or folic acid.

13. The composition of claim 12, wherein the first neurogenic agent is atorvastatin; and the second neurogenic agent is buspirone, ribavirin, tacrine, azakenpaullone, or folic acid.

14. A method of treating a nervous system disorder in a mammalian subject in need thereof, the method comprising administering a neurogenic amount of the composition of claim 1 to the mammalian subject, thereby treating the nervous system disorder.

15. The method of claim 14, wherein the nervous system disorder is related to a nerve cell trauma, a psychiatric condition, a neurologically related condition, or any combination thereof.

16. The method of claim 14, wherein the nervous system disorder is a neural stem cell disorder, a neural progenitor cell disorder, a degenerative disease of the retina, an ischemic disorder, or any combination thereof.

17. The method of claim 15, wherein the psychiatric condition is an affective disorder, depression, major depression, treatment refractory depression, hypomania,
panic attacks, anxiety, excessive elation, bipolar depression, bipolar disorder, seasonal mood disorder, schizophrenia, psychosis, lissencephaly syndrome, anxiety, an anxiety syndrome, an anxiety disorder, a phobia, stress, a stress syndrome, a cognitive function disorder, aggression, drug abuse, alcohol abuse, an obsessive compulsive behavior syndrome, a borderline personality disorder, non-senile dementia, post-pain depression, post-partum depression, cerebral palsy, post traumatic stress disorder, or any combination thereof.

18. The method of claim 17, wherein the psychiatric condition is depression.

19. The method of claim 17, wherein the psychiatric condition is post traumatic stress disorder.

20. The method of claim 15, wherein the nerve cell trauma is from an injury or a surgery.

21. The method of claim 20, wherein the injury or the surgery is related to: retinal injury or surgery, cancer treatment, infection, inflammation, an environmental toxin, or any combination thereof.

22. The method of claim 15, wherein the neurologically related condition is a learning disorder, autism, an attention deficit disorder, narcolepsy, a sleep disorder, a cognitive disorder, epilepsy, temporal lobe epilepsy, or any combination thereof.

23. The method of claim 14, wherein the mammalian subject is a human.

24. A method of increasing neurogenesis or neurodifferentiation of a vertebrate cell or a vertebrate tissue, the method comprising contacting the cell or the tissue with the composition of claim 1, in an amount that is effective to increase neurogenesis or neurodifferentiation of the cell or the tissue.

25. The method of claim 24, wherein the cell or tissue is mammalian or human, and wherein the contacting step is performed in vitro.
Atorvastatin

Neuronal Differentiation (TUJ1)

- Atorvastatin

Figure 1: Human Neurogenesis Assay
Figure 2: Human Neurogenesis Assay:
Atorvastatin + Buspirone

Neuronal Differentiation (TUJ1)

- • Atorvastatin
- ■ Buspirone
- ♦ Combination

Percent of Positive Control

Conc (M)

10^{-11.5} 10^{-10.5} 10^{-9.5} 10^{-8.5} 10^{-7.5}
Figure 3: Human Neurogenesis Assay:
Atorvastatin + Ribavirin

Neuronal Differentiation (TUJ1)

Percent of Positive Control

Conc (M)

- - Atorvastatin
■ - Ribavirin
• - Combination
Figure 4: Human Neurogenesis Assay:
Atorvastatin + Tacrine

Neuronal Differentiation (TUJ1)

- Atorvastatin
- Tacrine
- Combination

Percent of Positive Control

Conc (M)

$10^{-1.5}$  $10^{-1.0}$  $10^{-0.5}$  $10^{-0.0}$  $10^{0.5}$
Figure 5: Human Neurogenesis Assay: Atorvastatin + Azakenpaullone

Neuronal Differentiation (TUJ1)

- Atorvastatin
- Azakenpaullone
- Combination

Percent of Positive Control

Conc (M)

10^{-1.5} 10^{-1.0} 10^{-0.5} 10^{-0.0} 10^{-0.5} 10^{-0.0} 10^{0.5} 10^{1.0}
Figure 6: Human Neurogenesis Assay: Atorvastatin + Folic Acid

Neuronal Differentiation (TUJ1)

- • Atorvastatin
- □ Folic Acid
- ⬤ Combination

Percent of Positive Control vs. Concentration (M)
Figure 7: Human Neurogenesis Assay: Atorvastatin + Serotonin

Neuronal Differentiation (TUJ1)

- • Atorvastatin
- ■ Serotonin
- ◇ Combination

Percent of Positive Control

Conc (M)

$10^{-11.5}$  $10^{-10.5}$  $10^{-9.5}$  $10^{-8.5}$  $10^{-7.5}$
Figure 8: In Vivo Neurogenesis
Atorvastatin increases BrdU+ cell proliferation/survival

Treatment ID Key
1: Vehicle (n=11)  
2: Fluoxetine 5mg/kg (n=12)  
3: Fluoxetine 15mg/kg (n=9)  
4: COMBO (n=10)  
5: Atorvastatin 10mg/kg (n=11)

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Figure 9: In Vivo Neurogenesis

Atorvastatin combined with fluoxetine increases the neuronal differentiation rate of BrdU+ cells
Figure 10: In Vivo Neurogenesis

Atorvastatin combined with fluoxetine increases the number of newborn neurons (similar to fluoxetine)

![Graph showing new neuron estimation](image)

**Treatment ID Key**
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2. Fluoxetine 5mg/kg (n=11)
3. Fluoxetine 15mg/kg (n=8)
4. COMBO (n=9)
5. Atorvastatin 10mg/kg (n=11)

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Figure 11
Combination Indices
(Index < 1 Indicates Synergy)

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